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The use of hypothermia in the closure of atrial septal defects in children

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The beneficial effects which could be expected from the use of hypothermia in cardiac operations were initially appreciated and demonstrated by W. G. Bigelow.[1] The method was utilized by F. J. Lewis in the performance of the first successful "direct-vision" repair of an atrial septal defect in September, 1952.[12] At the present time, 3 different surgical methods are widely used to correct atrial septal defects—the atrial well, cardiac bypass, and general body hypothermia.

The purpose of this article is to review our experience with the method of general hypothermia for the closure of atrial septal defects in children. At the end of June, 1960, 157 patients with atrial septal defects had been operated upon at The Hospital for Sick Children, Toronto; hypothermia had been used in 105 of the operations (Table I). Atrial septal defects associated with total anomalous pulmonary venous drainage or with a separate ventricular septal defect are excluded from this review.

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ISOLATED OSTIUM SECUNDUM ATRIAL SEPTAL DEFECT

Signs and symptoms. The ages of the 95 children at time of operation varied from 2 to 15 years; the average age was 9 years. Fifty-nine were girls and 36 were boys.

Although the usual complaint was of increased shortness of breath on exercise, over one-third of the children had no symptoms. The physical signs of this defect have been well described elsewhere. Mild congestive failure was present in only 3 children and cyanosis on effort in only one.

All but 2 showed some variant of the incomplete right bundle branch block pattern in the electrocardiogram. The mean axis of the QRS complex lay between +60° and −150° in all and in 75 per cent between +60° and +150°. The frontal vector

Table I. *The use of hypothermia in 105 cases of atrial septal defect*

Defect	*No. of patients operated upon*	*No. of cases in which hypothermia used*
Isolated ostium secundum atrial septal defect	102	95
Ostium secundum atrial septal defect plus partial anomalous pulmonary venous drainage	10	2
Ostium secundum atrial septal defect plus pulmonary stenosis	6	4
Ostium secundum atrial septal defect plus mitrial valve abnormality	3	1
Ostium primum atrial septal defect	3	2
Ostium primum atrial septal defect plus cleft mitral valve	17	0
Ostium primum atrial septal defect plus cleft mitral valve and tricuspid valve	3	1
Common atrioventricular canal	13	0
Totals	157	105

was inscribed in a clockwise direction in all cases in which it could be computed.[4]

Preoperative right-heart catheterization was performed in 92 of the 95 patients; in only 3 was the systolic pressure in the pulmonary artery over 50 mm. Hg. At operation, 73 of the defects were located in the central portion of the atrial septum and 2 were found in the superior portion. In 18 the inferior margin extended to the entrance of the inferior vena cava (Fig. 1).

Method of operation. As experience was gained, the surgical technique was modified. Only the present technique is described.

The children were anesthetized with thiopental (2.5 per cent) and intubated under succinylcholine relaxation (1 mg. per 3 pounds).[2] They were ventilated with a nitrous oxide–oxygen mixture until spontaneous respiration returned. Halothane was then added and was used as required until the time of inflow occlusion.[2] From then on, usually nitrous oxide only was required. Respiratory control was established as soon as operation was begun and hyperventilation maintained until the chest was closed.

The patients were cooled within a refrigerating blanket and ice bags were added to the axillary and inguinal areas. The skin was not moistened. Both rectal and esophageal temperatures were monitored and the cooling was controlled so that the esophageal temperature did not drop below 29° C. and the rectal temperature below 30° C. The temperature at which the operation was begun varied somewhat with the size of the child, but was usually around 33° to 34° C. At the time of inflow occlusion, the esophageal temperature was 29° to 31° C. and warming had commenced.

The chest was opened with a sternum-splitting incision; neither pleural cavity was entered. The superior and inferior venae cavae were encircled by umbilical tapes which were passed through rubber tubes and used as tourniquets. Two parallel rows of silk sutures were inserted in the lateral wall of the right atrium (Fig. 2, *A*). Traction on the ends of these sutures aided in the application of the Satinsky clamp and was a safety factor in case the clamp should slip once the atriotomy had been made. After the right atrium had been opened within the confines of the clamp, stay sutures of fine silk were inserted. Blind finger exploration of the interior of the right atrium is no longer performed.

The operating table was then rolled to the patient's left, so as to place the atrial septum in a horizontal plane. Before the cavae were occluded, the anesthetist further oxygenated the patient and also injected a small quantity of relaxant in order to prevent diaphragmatic movements while the heart was open. At this stage, 500 ml. of heparinized blood was attached to the intravenous tubing and was used to replace the blood lost during the cardiotomy.[18] As soon as the cavae had been occluded, the entire heart was firmly compressed several times so as to empty it of blood; the Satinsky clamp was then removed. The aorta, pulmonary artery, and pulmonary veins were not occluded; the coronary arteries were not perfused; and a cardioplegic agent was not injected.

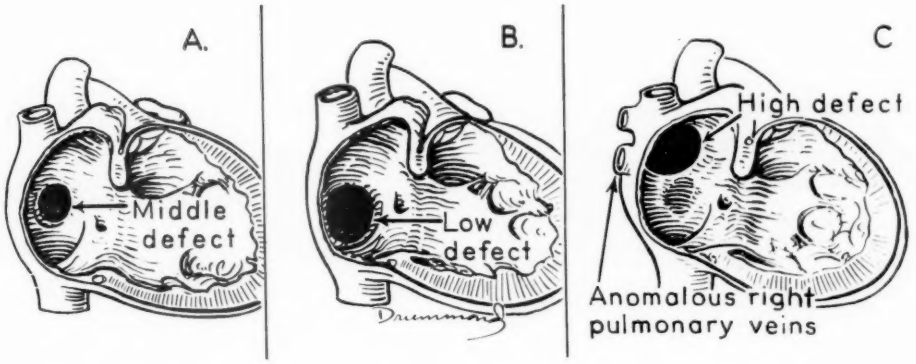

Fig. 1. Three varieties of ostium secundum atrial septal defect.

The sucker used to empty the right atrium of blood and to control the slight venous flow which comes from the coronary sinus was fashioned so that it would act as a retractor for the right edge of the incision (Fig. 2, *B*). A similarly shaped hollow retractor was used for the left side of the incision and through it carbon dioxide was passed.[15] Thus the operation proceeded in a dry field, under a blanket of carbon dioxide, and with a minimum of instruments.

The atrial septal defect was visualized, the superior end was picked up, and a waxed No. 2-0 silk suture inserted. Traction on this suture allowed a more accurate definition of the important inferior end of the defect. It is not our practice to excise the eustachian valve of the inferior vena cava, but rather to display its anatomy and then, if the atrial defect extends down to the inferior vena cava, to place the lower suture on the left atrial side of the septum. Care was taken to avoid the region of the coronary sinus lest conduction disturbances occur. The lower stitch was then continued to an over-and-over fashion to the superior end of the defect. The knot which united it to the upper suture was formed but it was not tied until all air and carbon dioxide had been extruded from the left atrium. This was accomplished by the anesthetist by inflation of the lungs while the surgeon held the superior portion of the atrial septal defect open. The knot was then "snugged up" under the protection of the blood. The inferior vena cava was released first in order to double-check its patency. With the long suture and the 2 stay sutures held up, the Satinsky clamp was easily reapplied as the right atrium filled with blood.

The right atriotomy was closed by a continuous running silk suture. The pericardial cavity was drained by a No. 16 Fr. rubber catheter and the anterior mediastinum by a No. 20 Fr. polyethylene catheter. The lower half of the pericardium was closed with silk,

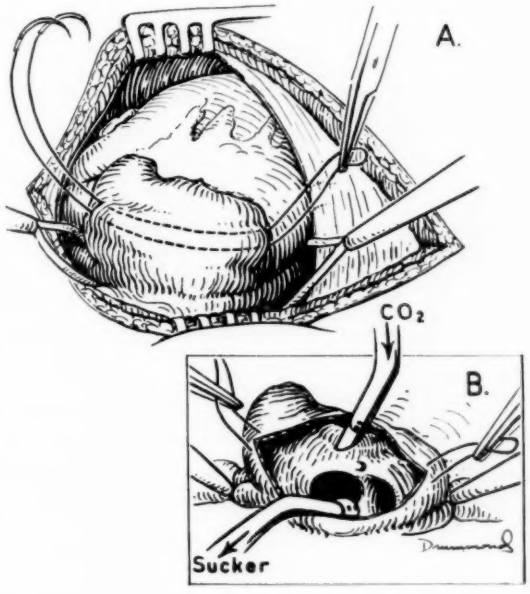

Fig. 2. *A*, The insertion of 2 parallel rows of sutures in the lateral wall of the right atrium. *B*, The use of a right-angled sucker and cannula for delivery of carbon dioxide as retractors.

the sternum with wire. Hemostasis was meticulous. Intradermal wire was used for the skin closure.

Results of operation. The morbidity resulting from this procedure was low. There have been 4 cases of wound infection of which only one, osteomyelitis of the lower sternum, was a cause for prolonged hospitalization. One patient developed a staphylococcal pericarditis which responded rapidly to treatment. No child in this series required postoperative bronchoscopic suction. Heart block did not occur, although 1 child had atrial flutter for 3 months.

There have been 3 cases of cerebral gas emboli, 1 with air and 2 with carbon dioxide. In 2 of the children the gas was also noted in the coronary arteries and ventricular fibrillation occurred during operation. The children remained unconscious for 1 to 3 days postoperatively. They were all treated by prolonged hypothermia, as described by Williams.[19] All have recovered completely and have no detectable neurological sequelae.

Incomplete closure of the atrial septal defect was suspected clinically in 2 children and proved by postoperative cardiac catheterization. In 1 child, prolonged cardiac massage had been required to overcome ventricular fibrillation and we believe that the recurrence occurred at this time. This recurrence was large enough to demand a second operative procedure. The other recurrence was small (10 per cent rise in atrial oxygen saturation) and further treatment was not recommended.

In the entire series of 95 patients, there was only 1 death from the initial operation. This child died 16 hours after the operation (September, 1957) from cardiac tamponade. The child with the severe recurrence described was operated upon a second time 2 years after the initial procedure; she died on the operating table from an atrial tear which occurred during the thoracotomy. Thus, the hospital mortality rate from this procedure was 2.1 per cent.

The other 92 patients are thought to be entirely cured of the defect. Postoperative cardiac catheterization has been performed on 14 other patients and in none has there been evidence of a persistent left-to-right shunt.

ATRIAL SEPTAL DEFECT AND PULMONARY STENOSIS

We have operated upon 6 children with a combination of valvular pulmonary stenosis and atrial septal defect of the ostium secundum type. Cardiac bypass was used in 2, hypothermia in 4. The preoperative systolic gradient across the pulmonary valve varied from 52 mm. Hg to 77 mm. Hg. In the first period of inflow occlusion (average of 3 minutes), the pulmonary artery was opened and the pulmonary valve dealt with. With a second period of inflow occlusion (average of 4 minutes), the atrial septal defect was closed. All 6 children have done well. We prefer to use hypothermia in the correction of this lesion, as the coronary flow is then at a minimum and the pulmonary valvotomy is performed in a much drier field.

ATRIAL SEPTAL DEFECT ASSOCIATED WITH PARTIAL ANOMALOUS PULMONARY VENOUS DRAINAGE

Of the 10 patients operated upon, hypothermia has been used in only 3. In each case in which hypothermia was used, the presence of the anomalous venous drainage was not suspected preoperatively. One child had come to operation without a right-heart catheterization.

In the first case, 2 anomalous right pulmonary veins were present—1 entering the right atrium and 1 entering the superior vena cava. The atrial septal defect was of the high "sinus venosus" type; a left superior vena cava was also present. The defect was corrected by ligation of the right superior vena cava below the azygos vein and above the entrance of the superior pulmonary vein and by then sewing the anterior edge of the atrial septal defect to the lateral wall of the right atrium so that the inferior pulmonary vein and the right

superior vena cava were directed into the left atrium. A 5-minute period of inflow occlusion was required.

In the second case, the right superior pulmonary vein entered the upper portion of the right atrium and was associated with a centrally placed atrial septal defect. The defect was enlarged superiorly to give a longer anterior margin which was then sewn to the lateral wall of the right atrium so as to direct the blood from the pulmonary vein into the left atrium. A 7½-minute period of inflow occlusion was required.

In the third case, 3 veins from the right lung entered the right atrium through separate ostea and the atrial septal defect was again centrally placed. After careful assessment of this situation by finger palpation, it was decided to reoperate with the use of cardiac bypass. This anomaly was corrected uneventfully 2 weeks later.

Although neither of the 2 patients in whom the defect was corrected under hypothermia has undergone postoperative catheterization, they have no clinical evidence of a persistent defect and no evidence of superior vena caval obstruction. In spite of the good result obtained in these 2 cases, we believe that all such patients should (if diagnosis is made preoperatively) be operated upon with cardiac bypass. A pulmonary vein entering the superior vena cava will be diagnosed on careful catheterization, but one entering the right atrium may be missed. If so, and it is encountered at operation being performed with the technique of general hypothermia, it can usually be dealt with satisfactorily. We agree with the suggestion of F. J. Lewis that a single vein entering high in the superior vena cava might well be left untouched.[10]

OSTIUM SECUNDUM ATRIAL SEPTAL DEFECT ASSOCIATED WITH ABNORMAL MITRAL VALVE

We have operated upon only 2 patients with Lutembacher's syndrome (atrial septal defect plus mitral stenosis). Cardiac bypass was used. One other patient, a 9-year-old boy suffering from rheumatic mitral incompetence and an atrial septal defect of secundum type, was operated upon under hypothermia in November, 1957. Only the atrial septal defect was corrected and the child has done well since the operation. With the methods now available to correct abnormal mitral valves, cardiac bypass would of course be used in all such cases.

THE OSTIUM PRIMUM GROUP

The electrocardiographic criteria required to accurately diagnose the ostium primum atrial septal defect were not crystallized until late in 1958.[8] Prior to that time, 3 members of this group had been operated upon with the hypothermic method.

In October, 1956, a 13-month-old girl with pulmonary hypertension and severe symptoms was operated upon with hypothermia of 29° C. She died during the operation and postmortem examination showed an ostium primum atrial septal defect with associated complete clefts in the aortic leaflet of the mitral valve and the septal leaflet of the tricuspid valve.

In June and October, 1958, 2 boys, age 12 and 13, were brought to operation for ostium secundum defects. There was no preoperative evidence of mitral or tricuspid valvular insufficiency. At operation under hypothermia, the defects were found to be of the ostium primum type and both were repaired by direct suture. Although the mitral and tricuspid valves were only superficially examined at operation there is still no sign that they are incompetent. Both children are asymptomatic and although only one has undergone postoperative catheterization, both the defects appear to be completely closed. On rechecking the electrocardiograms, the axes of the QRS complex were seen to be –70° and –130° and the frontal vectors were inscribed in a counterclockwise direction mainly above the horizontal plane.

All patients with the ostium primum defects who come to operation today are operated upon with the aid of cardiac bypass. In this manner the valves can be carefully examined and repaired, a patch

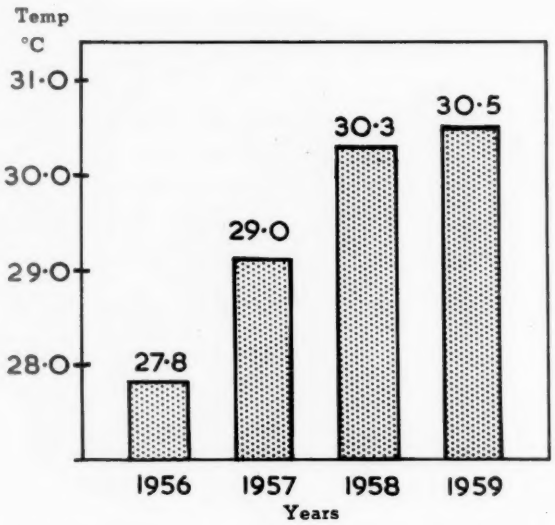

Fig. 3. The change in degree of hypothermia utilized during the closure of atrial septal defects.

may be used in the atrial septal defect if necessary, and the conducting tissue can be carefully guarded.

DISCUSSION

The degree of hypothermia. In the first few cases in which hypothermia was used, there was a tendency to allow the body temperature to drift too low. The ease of producing hypothermia in a child, the practice of wetting the skin during cooling, and the belief that temperatures of 24° to 27° C. were safe, were major factors contributing to this tendency.

Table II and Fig. 3 illustrate the gradual change in the degree of hypothermia employed. Today, instead of a rectal temperature of 27° to 28° C. the lowest temperatures sought are an esophageal temperature of 30° to 31° C. and a rectal temperature of 31° to 32° C. At such temperatures, the oxygen consumption of the body is reduced to almost half that of normal and periods of circulatory occlusion of up to 8 minutes are quite safe.[1]

Use of cardioplegic agents. In June, 1957, Lam[9] reported the use of acetylcholine to produce cardiac arrest during intracardiac operations with the aid of cardiac bypass. By the production of cardiac arrest, a still field was obtained and the oxygen requirements were reduced. This technique was used in 14 children operated upon with general hypothermia during the period of May, 1957, to August, 1958. The practice was discontinued after it was seen that the duration of inflow occlusion was lengthened and the incidence of ventricular fibrillation increased (Table III). Neostigmine has not been used.

The incidence of ventricular fibrillation in the last 70 patients operated upon without arrest has been 8 per cent (6 cases). The incidence of ventricular fibrillation described by Swan and associates[17] after the use of neostigmine was 12 times in 100 patients. Evan Bedford and his group[3] have reported an incidence of ventricular fibrillation of 2 out of 40 patients in whom neostigmine was used. In both series, adult patients were included.

The use of coronary perfusion. As the heart of each patient in this series has either produced an adequate output immediately after the release of the inflow occlusion (80 cases) or else has responded quickly to cardiac massage and defibrillation (15 cases), we do not believe that coronary perfusion is necessary.[13, 16] The common use of "hypoxic arrest" in cardiac bypass has shown that no true damage is done to the myocardium during such a short period of circulatory arrest. If arrest of longer than 8 minutes is required, then the repeated inflow occlusion technique described by Johnson[7] is more advisable. Our comments in this matter are colored, of course, by the fact that all the patients in our series were children. The myocardium of adults may require more protection.

Table II. *The changing level of hypothermia used during the surgical repair of isolated ostium secundum atrial septal defects*

Year	*Average lowest rectal temperature (C.)*	*% patients cooled to under 30° C. (rectal)*
1956	27.8	100
1957	29.2	86
1958	30.3	38
1959	30.5	3

Table III. *The use of acetylcholine arrest in the repair of ostium secundum atrial septal defects*

	No. of cases	*Ventricular fibrillation*	*Time of inflow occlusion*
No arrest	81	10 (12%)	4 min. 10 sec.
Acetylcholine arrest	14	5 (36%)	6 min. 20 sec.

Occlusion of other vessels. It is not necessary to occlude the pulmonary veins,[11] as the blood level remains constant in the left atrium and blood does not enter the operative field unless the anesthetist inflates the lungs. Some authors advocate clamping the aorta low enough to occlude the coronary vessels in order to reduce coronary sinus venous return, to avoid coronary air embolism, and to maintain tachycardia.[9, 16] The coronary sinus return in our children has been found to be very limited in amount and easily handled by the sucker. If any air or carbon dioxide is trapped in the left side of the heart, then perhaps it is better to have it enter the coronary rather than the cerebral arteries; in the former location it can be massaged out again.[5] We see no need to occlude the pulmonary artery.[11, 17] It has not been our practice to temporarily occlude the carotid vessels as the circulation is restored; this procedure may be indicated in view of our 3 cases of cerebral air embolism.

The operative approach. In January, 1958, the approach was changed from a right thoracotomy with an extension across the sternum, but not into the left pleural cavity, to a sternum-splitting incision. This approach is rapid, there is little bleeding, excellent exposure is obtained, and postoperative pain and pulmonary complications are minimized. Its main disadvantage is cosmetic, for a scar is left at the base of the neck—a scar which has a great tendency to keloid formation. It is our hope that the use of an intradermal wire will improve the appearance of this scar. Wound infection is rare in children and the one patient with sternal osteomyelitis responded rapidly to adequate treatment.

After trying several methods of draining the pericardium and mediastinum after this approach, we have settled on the one described in the section on surgical technique.

Completeness of closure. Ten of the first 19 children with isolated ostium secundum defects closed by this technique were catheterized postoperatively. The residual defects demonstrated in 2 patients had both been suspected clinically prior to catheterization. Seven other patients have been catheterized postoperatively and none has shown evidence of an incomplete closure.

The advantages and disadvantages of the method. Excellent results have been reported from centers where the "open-well" technique of Gross has been used.[6] McGoon and associates[14] report 51 instances of atrial septal defects closed by this method with no deaths and insignificant morbidity. We have had no experience with such a method, but believe that the ability to see the defect must add some advantages in both ease and completeness of closure.

Cardiac bypass undoubtedly has some advantages. Unforeseen complicating factors such as anomalous veins, abnormal mitral or tricuspid valves, or ostium primum defects can be handled more safely. With the present accuracy of cardiologic diagnosis, however, such cases will rarely be encountered unexpectedly. If they are, most of them can be handled satisfactorily within the time limits imposed by this technique. The fact that some cannot is the main criticism of the hypothermic technique.

The advantage of cardiac bypass must be compared with such disadvantages as the quantity of fresh blood required, the lengthened operating time, the postoperative bleeding problems, and other problems intrinsic to a more complicated technique.

SUMMARY

The experience of the group at The Hospital for Sick Children, Toronto, in the use of hypothermia for the closure of atrial septal defects is presented. One hundred and

five children have been operated upon with this technique up to the end of June, 1960. The modifications of the technique as used in this hospital are described and discussed.

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ADDENDUM

Since this paper was submitted for publication an additional 45 children have undergone operative closure of atrial secundum defects with no deaths and no recurrences (no recatheterization).

Lung and heart complications of the treatment of hydrocephalus by ventriculoauriculostomy

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For over half a century[9] the ideal surgical palliative treatment for hydrocephalus has consisted of shunting excess cerebrospinal fluid into the blood stream. There have been progressive technical advances in this field, with use of segments of veins,[18] arteries,[2, 6, 13, 15] rubber tubes,[5, 10] polyethylene tubes,[12] ball valves with tetrafluorethylene tubes,[20] and, more recently, the Spitz-Holter valve with nonwettable tubing which enables excess cerebrospinal fluid to be drained directly into the heart.

A large number of children have now been treated with the Spitz-Holter valve,[4, 16, 17] but the old problem of occlusion of the shunt channel appears in some cases to be replaced by a new series of complications. Two of Anderson's[1] series of 36 children died with pulmonary embolism. Three of Carrington's[4] series of 50 children died with septicemia, and 8 of MacNab's[16] 60 children had clot formation in the superior vena cava and heart.

We have become increasingly aware of a new pattern of pathologic lesions which have developed as a result of the cerebrocardiac shunts and the present paper is an attempt to describe them.

CASES AND FINDINGS

The material studied came from necropsies on 15 patients with hydrocephalus in which ventriculoauriculostomy with the Spitz-Holter valve had been performed. The children were from a series of over 100 so treated by Mr. R. B. Zachary in the Children's Hospital, Sheffield. In all but 2 of the cases the hydrocephalus was associated with a meningomyelocele and its associated deformities. The other 2 cases appeared to be primary hydrocephalus, probably due to aquiductal deformities. Death occurred between the ages of 18 days and 2 years, 10 months. The valve had been in situ from between 3 days and 2 years, 2 months.

Some details of the cases and the gross necropsy findings are presented in Table I. In the 15 children, 7 only showed necropsy evidence of meningitis, and in 5 of these 7 there was evidence of infection in the lung with emboli. In one of the latter, death occurred 11 days after the insertion of the valve.

The lesions found fall into 2 groups, cardiac and pulmonary. The cardiac lesions included partial or complete occlusion of the veins entering the right auricle, and thrombi of varying size attached to the end of the catheter, auricular wall, or to the tricuspid valve. The lung lesions included massive pulmonary alveolar hemorrhage in a child dying 4 days after insertion of the valve, multiple emboli of great variation in size and number, focal arteritis, and 1 peculiar case of hemosiderosis.

The lesions which were discovered are discussed in the order of their incidence (Table II).

Emboli in the pulmonary circulation. Multiple emboli were found in pulmonary vessels in all but 1 child, who died with massive pulmonary hemorrhage 4 days after insertion of the valve. In some cases the emboli were obviously recent and lay with-

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Table I. *Details of the gross necropsy findings of 15 children who died after ventriculoauriculostomy with the Spitz-Holter valve*

Age at death	*Period valve had been in situ*	*Valve tube entering auricle (Spitz-Holter valve)*	*Postmortem findings*	
			Heart	*Lungs*
2 yr., 10 mo.	2 yr., 2 mo.	Thrombosis of right jugular vein and innominate vein; no thrombus around catheter tip	Ulceration of endocardium of right auricle, 10 by 10 mm., with vegetation	Emboli with vascular occlusions but no gross infarction
18 days	5 days	End of tube entered tricuspid valve; no thrombi	No gross lesion	Recent emboli; small areas of vasculitis
11 mo.	7 mo.	Thrombus around catheter tip	Vegetations on tricuspid valve and right auricle wall	Massive pulmonary thrombosis
1 mo.	6 days	Thrombus around catheter tip	Acute pericarditis, endocarditis, endocardial ulceration	Septic infarcts; massive pulmonary thrombosis
1 yr.	5 mo.	Thrombosis in superior vena cava and innominate vein; catheter clear	Thrombus on wall of right atrium passing through tricuspid valve	Pulmonary hemosiderosis; small emboli; intimal degeneration
2 mo.	11 days	Thrombosis in superior vena cava and innominate vein; catheter clear	No gross lesion	Suppurative emboli; pleurisy with effusion
10 mo.	8 mo.	No thrombi	No gross lesion	Terminal thrombosis
2 mo.	4 days	No thrombi	No gross lesion	Collapse of lung with massive intra-alveolar hemorrhage
3 mo.	2 mo.	Small thrombus around catheter	Ulceration of endocardium of right auricle; mural endocarditis, tricuspid valve vegetations	Recent and old organized emboli
1 yr.	7 mo.	Tip of catheter in inferior vena cava; thrombus only around catheter in superior vena cava	No gross lesion	Mural thrombi in pulmonary arteries; acute focal vasculitis; bronchopneumonia
5 mo.	5 wk.	Thrombus about tip of catheter	Thrombus attached to tricuspid valve	Suppurative emboli
2 yr., 4 mo.	2 yr.	Catheter had passed from left jugular vein up innominate vein on right side; old thrombosis of all these veins present	No gross lesion	Multiple nonsuppurative emboli; *Torula histolytica* infection
8 mo.	4 mo.	Thrombus around tip of catheter	No gross lesion	Suppurative emboli
15½ mo.	8 mo.	Valve removed just before death; thrombosis of left and right jugular vein and right subclavian vein	No gross lesion	Suppurative emboli
8 mo.	3 mo.	Valve removed just before death	No gross lesion	Multiple nonsuppurative emboli; bronchopneumonia

in the lumina of medium-sized arteries (Fig. 1, *A*), but in the majority of instances they completely occupied small arteries and showed varying degrees of organization. Thus it is not certain whether many of the small lesions were emboli or local thrombus formations.

The changes in the surrounding tissues varied considerably. In many instances there appeared to be no edema or cellular infiltration of the vessel walls or surrounding tissues although the emboli were vascularized and being eliminated.

Occlusion of veins entering the heart. In every instance the catheter entering the heart was surrounded by a collar of dense, fibrinous material as it lay within the jugular vein. This collar extended varying distances down the catheter into the auricle. In several instances the clot had propagated from the jugular into the innominate and subclavian veins. In 1 case the catheter had passed from one innominate vein to the other and the whole of the superior vena caval system appeared to be completely occluded.

Thrombosis around the distal end of the catheter. As mentioned, the catheter was always surrounded by a collar of fibrinous material, but the end of the tube did not appear to be occluded. Attached to the end of the fibrinous collar were variable masses of fibrinous clot and Fig. 2 shows one of these. This was a large mass which entered and obstructed the tricuspid valve and apparently caused clinical tricuspid incompetence.

In 1 case in which a large thrombus of this type was found, the clinicians had observed abnormal heart murmurs over the right side of the thorax and the presence of a thrombus occluding the tricuspid valve was diagnosed before death.

In 2 instances there was no clot attached to the end of the catheter, but massive pulmonary embolism had occurred.

In surveying the cases, we gained the impression that the majority of the large pulmonary emboli came from fibrinous thrombi attached to the end of the catheter.

Table II. *Lesions in heart and lungs in 15 children who died after ventriculo-auriculostomy with Spitz-Holter valve*

Lesion	*No. of cases*
Multiple small "emboli" in pulmonary circulation	14
Complete or partial occlusion of veins entering heart	13
Thrombus around distal end of catheter	10
Other lesions of pulmonary vessels	
Early mycotic aneurysm formation	7
Periarteritis	8
Intimal degeneration	4
Thrombus formation on wall of right atrium with or without extension to tricuspid valve	6
Ulceration of auricular endocardium due presumably to trauma by catheter	4
Massive pulmonary embolism	2
Pulmonary hemosiderosis	1

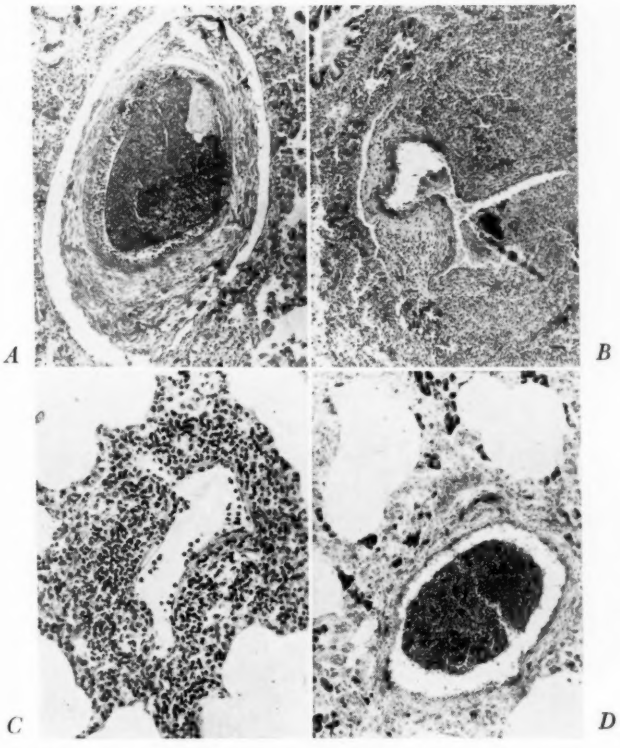

Fig. 1. *A,* Cross section of a medium-sized artery in lung which contains a thrombus. *B,* Artery in which part of the wall is necrosed. Black area is a mass of organisms. *C,* Small blood vessel in the lung which shows acute periarteritis. *D,* Lung which shows a blood vessel and alveoli. The section has been stained for iron. Black-stained cells are iron-containing macrophages in the alveoli. Black iron deposition can also be seen deep to the wall of the blood vessels almost in the center of the photograph.

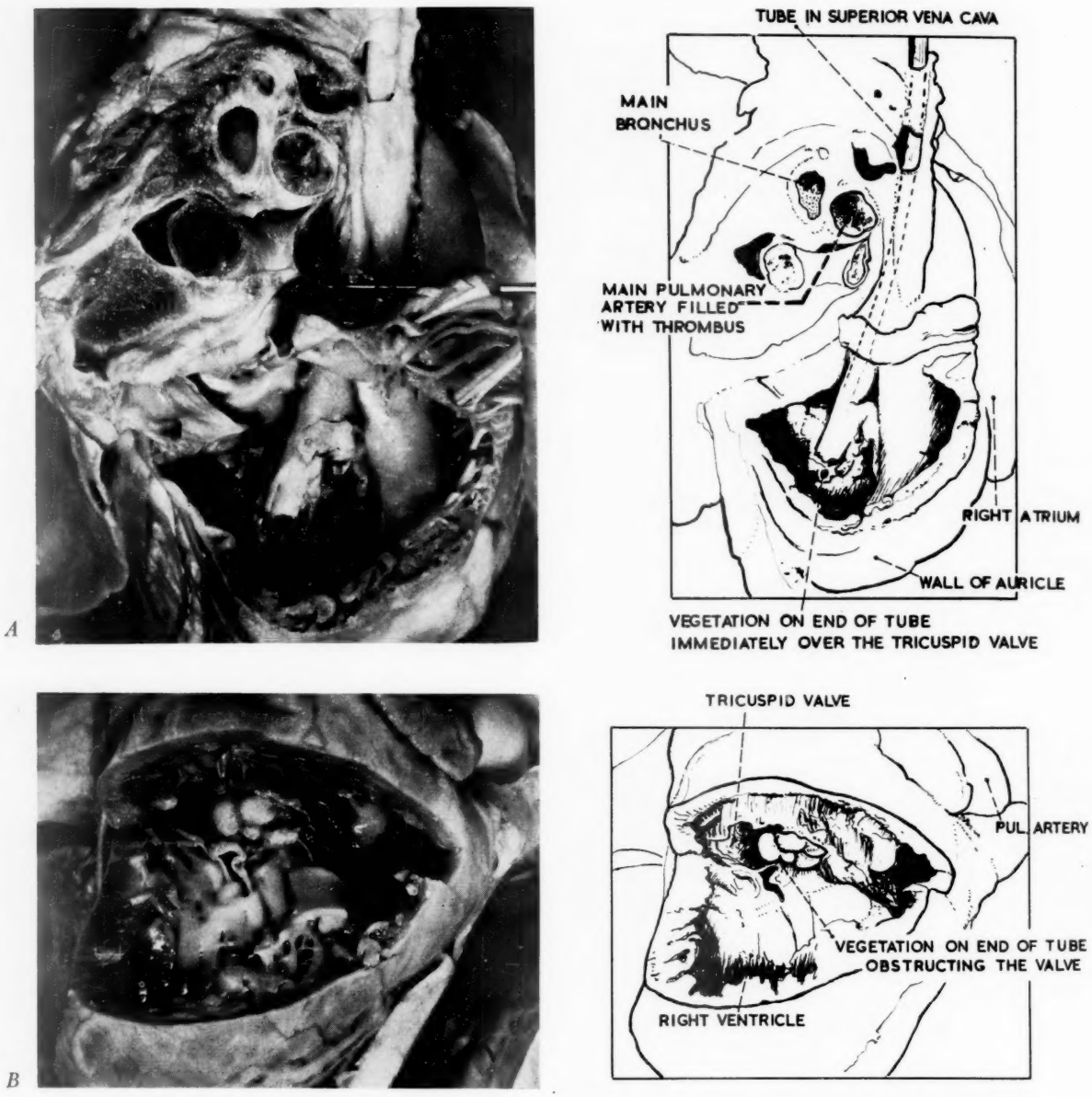

Fig. 2. *A,* The right lung cut across the hilum and the right atrium opened from above. The course of the catheter through the vena cava and entering the auricle can be seen, and a broken mass of thrombus is visible on the end of the catheter. The main pulmonary artery, adjacent to the main bronchus, is completely occluded by thrombus. *B,* The view looking up onto the free edge of the tricuspid valve through a wedge-shaped opening in the right ventricle.

Other lesions of pulmonary vessels.

Mycotic aneurism formation. In 7 cases intra-arterial thrombi were associated with suppuration, destruction of the arterial wall, and extension into the surrounding tissue. One such lesion is shown in Fig. 1, *B.*

Periarteritis. In several cases the first impression on superficial examination of the sections was that the lungs showed multiple areas of bronchopneumonia. Closer inspection showed that the local areas of inflammation were not associated with the bronchioles, but surrounded small blood vessels and in 8 cases multiple foci of periarteritis were found (Fig. 1, *C*). In these cases the vessels did not appear to contain thrombi and in some vessels cut longitudinally the periarteritis appeared to be completely focal

and quite independent of any local intimal change.

Intimal degeneration. In 4 cases, intimal degeneration in the form of swollen, thickened intimal cells was found. This intimal change was not associated with any inflammatory infiltration. The latter lesions, however, are difficult to interpret in the light of the artefact found at postmortem examination.

Thrombus formation on the wall of the right atrium. In 6 cases the wall of the right atrium contained one or more plaques of smooth, yellow vegetation. These areas were not propagated thrombi from the superior vena cava and appeared to have arisen at the site of some trauma to the auricle. In several instances it was difficult to understand how trauma from the catheter could have occurred. In 2 instances the vegetations had progressed on the surface of the tricuspid valve and partially occluded the lumen.

Local pericarditis. In 1 instance in which catheter trauma was likely, there was local pericarditis over the area of vegetation.

Massive pulmonary thrombosis. In 2 cases the child died suddenly and unexpectedly and the major necropsy finding was complete occlusion of the pulmonary arteries by embolus. These emboli had apparently come from thrombotic masses already described around the end of the catheter in the auricle.

Pulmonary hemosiderosis. One child showed a remarkable clinical picture. After the insertion of Spitz-Holter valve and shunt, the child developed progressive anemia which necessitated repeated transfusions. At necropsy the lung was found to be indurated and brown. Microscopy of sections stained for iron showed many iron-laden macrophages within the alveoli and deposits of iron in and around the walls of small arteries (Fig. 1, *D*). The site of periarterial iron deposition corresponded exactly with the areas of periarteritis found in other cases. No inflammatory changes were seen. Sections stained for elastic tissue did not convince us that there was any primary defect in structure of the lung and we were forced to conclude that there was some relationship between the presence of the cerebrocardiac shunt and the hemosiderosis.

DISCUSSION

The introduction of the Spitz-Holter valve appears to be associated with 2 groups of pathologic lesions in the heart and lungs; first, the local and embolic effects of thrombi on the end of the tube in the cardiac auricle, and second, lesions in the lung that appear to be independent of the presence of thrombi or embolism (that is, periarteritis, intimal degeneration, and possibly hemolysis and hemosiderosis). Since we do not know the constituency of cerebrospinal fluid throughout the history of these patients, we cannot say whether the changes in the pulmonary blood vessels are due to infected cerebrospinal fluid entering the pulmonary circulation or to a reaction of the vessel wall to what may be essentially a foreign cerebrospinal fluid protein.

The thrombotic lesions are more easy to understand and are probably of greater immediate clinical importance, as in 2 of the patients that died, cardiac signs developed with apparent tricuspid incompetence. Surgical interference and the removal of a large thrombus in the auricle appear to be a practical possibility.

The lesions that we have found in the lungs are very like those described in the older literature after endocarditis of the ductus arteriosus.[3, 7, 11] It is very important that pyrexia and periods of crepitations in the lung be treated seriously and not dismissed as being small areas of bronchopneumonia. If a child who has such a tube and shunt entering the auricle develops meningitis or pneumonia, it should be treated medically as acute bacterial endocarditis.

The patients discussed here are dead, but the frequency of small lesions in these cases suggests that similar lesions are probably present in children alive with these shunts. Unusual pulmonary and cardiac symptoms and signs are thus likely to occur in such cases and merit special clinical study.

SUMMARY

Children who die after ventriculoauriculostomy shunt with the Spitz-Holter valve showed the presence of multiple lesions in the pulmonary circulation.

In addition to emboli and thrombi, there were local arteritis, periarteritis, and mycotic aneurysm formation. One child had pulmonary hemosiderosis.

Large thrombi attached to the end of the auricular catheter had caused tricuspid incompetence.

With any clinical infection, particularly of the meninges and lungs in children treated with such shunts, an associated acute endocarditis should be suspected.

Photographs were taken by Mr. Rickus and the drawings were made by Mr. Foster.

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Measurement of arterial flow in the lower extremities with radioisotopes

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Radioisotopes have previously been used in attempts to determine the rate of blood flow in extremities. Their use was provoked by general dissatisfaction with the older methods of oscillometry, plethysmography, and colorimetry.

Radioactive sodium and I^{131}-labeled serum albumin have been the agents chiefly employed. Scintillation counters have proved most satisfactory as detection devices. Two general methods have been used; first, determination of the build-up of activity in a region after intravenous injection,[2, 5] and second, measurement of the rate of removal of a labeled diffusable local injection into the tissue.[4] Scintillation counters placed regionally are then used to determine the rate of build-up, or "wash-out," of the substances.

In practical application these methods have heretofore had 4 inherent deficiencies. First, in measuring build-up after intravenous injection the prolonged time needed to achieve intravascular mixing has led to sources of error. The slow mixing of the isotope reflects in late "contamination" of the curve which causes significant errors. Second, recently arterial injections of substances have been tried in order to diminish the mixing time.[1] Technical difficulties with this method, such as control of the speed of injection and geometric distortion produced by the injection, might impose a problem. In addition, if build-up curves were attempted over the lower leg after injection into the femoral artery, any pathologic process proximal to the point of injection might be missed. We have eliminated slow mixing as a source of error more simply by using a tourniquet technique. Third, dosage has also been a problem inasmuch as there are significant variations in the tissue–vascular space ratio in human beings, depending on obesity, muscle mass, and so forth. Fourth, the "wash-out" methods in which Na^{24} is chiefly employed have the disadvantage of being influenced too greatly by local conditions such as edema, spasm, and actual tissue distortion from the injection.[3]

The shortcomings of the methods mentioned with their apparent inaccuracies and procedural complexity have relegated them to the research laboratory. There has been a need for a relatively simple, accurate, and objective method of evaluating patients with claudication-like symptoms. We have developed a method which satisfies these prerequisites. The method has been effectively used as a screening device and as an adjunct to arteriography.

The first portion of our study was conducted on laboratory animals. The object was to produce controlled arterial insufficiency and determine the relative efficiency of the radioisotope build-up method in reflecting the degree of arterial insufficiency.

STUDIES IN DOGS

Method and materials. Twenty-seven dogs were studied in the laboratory under pentobarbital anesthesia. After heparinization, the

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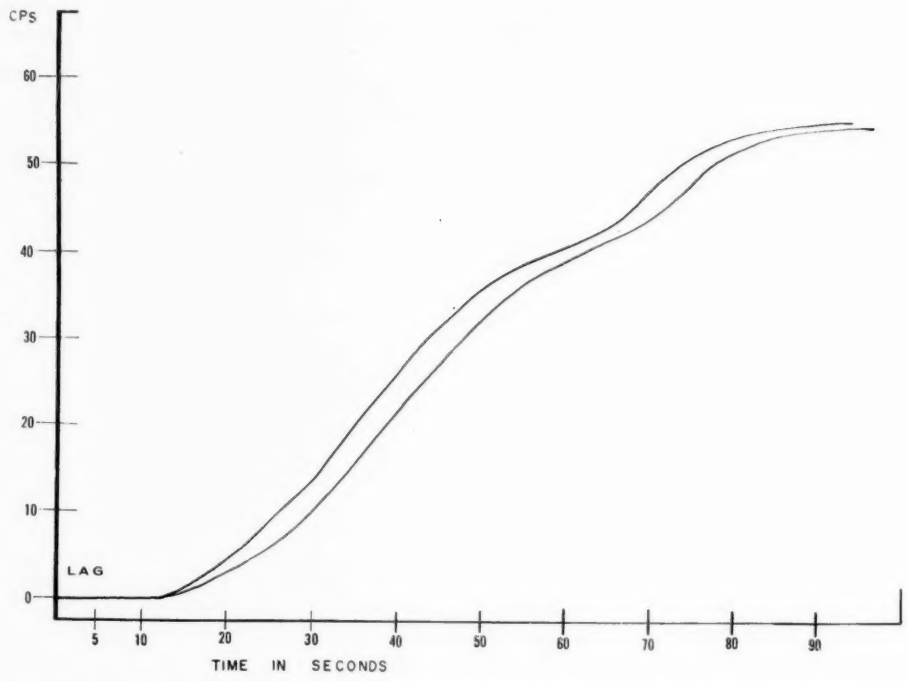

Fig. 1. This graph represents the uniformity of isotope response in 2 dogs of equal weight given equal dosages of I^{131}.

right femoral artery was cannulated to divert the blood through a recording flowmeter* and return it to the femoral artery at the level of the bifurcation of the profunda femoris. Readings on the flowmeter were interpreted in milliliters per minute. When the rate of flow had stabilized, albumin I^{131} was rapidly injected through a catheter placed high in the brachial vein. A probe scintillation counter† placed against the popliteal area of the right leg below the cannulated femoral artery then recorded the rate of build-up of radioactivity as arterial blood flowed into the leg.

Results. The curves obtained in normal dogs were found to have a striking geometric uniformity and displayed 4 different features (Fig. 1): (1) an initial lag period of 10 seconds, (2) a sharp primary rise reaching a plateau at 30 seconds, (3) a secondary upward slope, and (4) an end point achieved after 90 seconds which did not fluctuate.

The slope of the curve and the magnitude of the end point were directly proportional to the dosage of I^{131} per pound weight. Fig. 1 illustrates the identical response in 2 dogs of similar weight given equal dosages of the tracer.

We next attempted to produce arterial occlusion in the dog comparable to the syndrome seen in arteriosclerosis obliterans. After interruption of the generous collateral flow to the right leg, the iliac artery was partially occluded. The resultant degree of diminished blood flow in the leg was then measured with the mechanical flowmeter. After stabilization, the tracer was injected into the brachial vein in standard dosages. The degree of reduction in flow afforded by partial ligation of the iliac artery was reflected in the radioisotope build-up curve. Fig. 2 depicts the response in 4 animals which received 0.3 μc of I^{131} per pound. The upper curve is that of a normal dog. The 3 succeeding lower curves represent the graded slower response in animals with 75 per cent, 50 per cent, and 25 per cent of normal flow. It will be noted that the lag period and time to maximum response are progressively prolonged with increased oc-

*Rotameter and recording unit No. 45, Clifford Wilson, Indianapolis, Ind.

†NRD Radimax scintillation counter, NRD Instrument Company, St. Louis, Mo.

clusion and the slopes of the curves are lowered accordingly.

STUDIES IN HUMAN SUBJECTS

Materials and methods. We next attempted to apply this method to human beings. Sixty patients, both normal and abnormal, have been tested. Abnormal patients were those with arteriographically proved occlusive disease. Except for the omission of the mechanical flowmeter and substitution of direct needle puncture in an antecubital vein for the brachial vein cut-down, the procedure was the same initially as that used in the animal studies. Two-tenths of a microcurie per pound was found to be a safe, workable dose of the tracer material.

After injection of the tracer into the vein the response curves achieved over the lower leg were found to be similar to those found in dogs. The lag period was more prolonged, however, and it was noted that some of the patients with proved arterial occlusion had build-up curves not unlike those seen in the lower range in normal patients. This apparently was due to slower mixing of the tracer material which had been introduced by direct venipuncture to simplify the technique.

This error was obviated by application of an arterial tourniquet to the thigh of the leg being studied immediately prior to the injection and for a period of 2 minutes thereafter. A tourniquet pressure of 450 mm. was maintained during this period. There were no untoward effects from the tourniquet, even in patients with postoperative grafts. The use of the tourniquet allowed the isotope to be homogenously distributed everywhere except in the leg in which flow was being measured. Upon rapid release of the tourniquet, the tagged blood was suddenly allowed to flow into the leg and the geometry of the arterial bolus was reflected in counts per second by the recorder attached to the scintillation counter. Fig. 3 shows that the response in normal human subjects is extremely predictable.

Results. In 20 normal subjects tested by this method the lag time was found to vary only 2 seconds. The range was from 2.0 to 4.0 seconds. In 10 consecutively studied patients with proved occlusive disease the lag period varied from 10 seconds to infinity

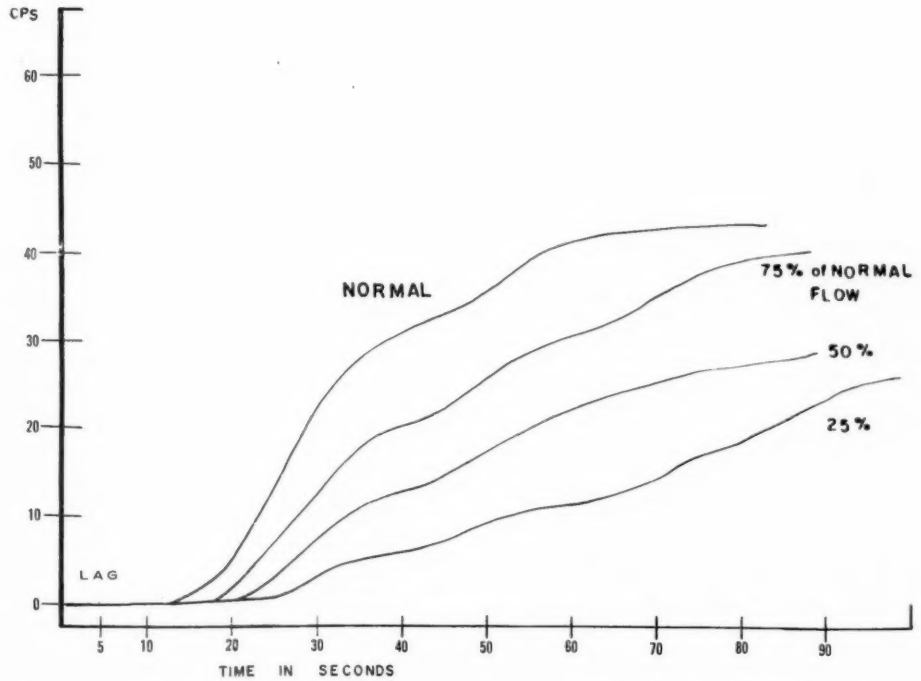

Fig. 2. Curves representing isotope response in a normal animal contrasted to the responses achieved in dogs with progressive occlusion of the femoral artery.

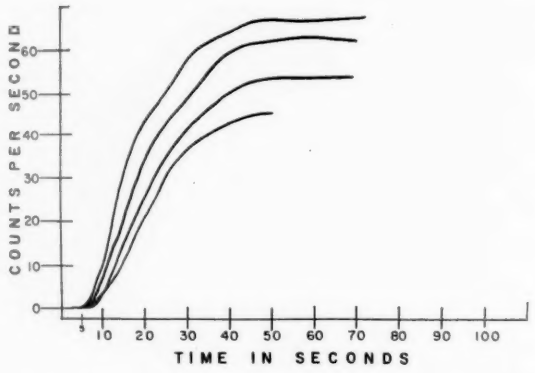

Fig. 3. Isotope response pattern in normal human subjects. Note the relatively short lag time. The time needed to reach maximum concentrations ranges from 30 to 40 seconds.

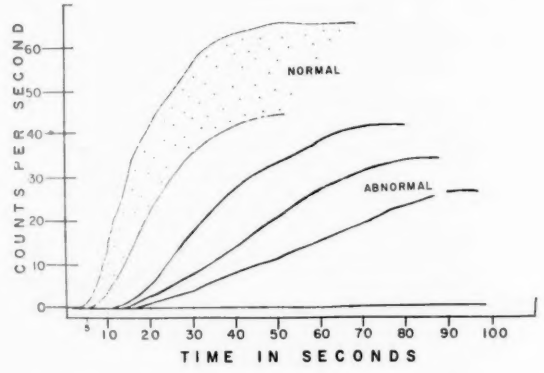

Fig. 4. Illustration of the range of isotope response in normal subjects as contrasted to patients with proved arterial occlusive disease. Note the increasing lag time and delay of maximum response with disease.

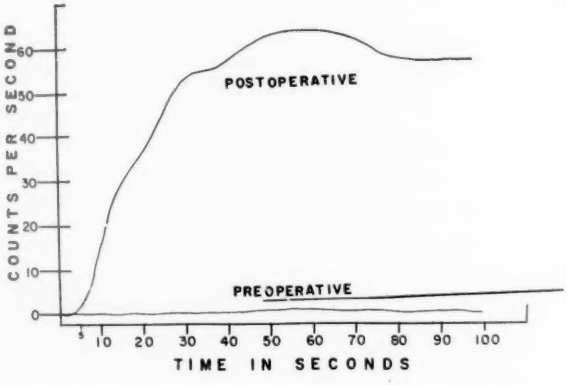

Fig. 5. Pre- and postoperative results in a patient with occlusion of a femoral graft. The graft was replaced surgically and the build-up curve improved dramatically.

(Fig. 4). This characteristic tends to separate clearly the normal from the abnormal group.

Normal patients were found to have a steeper slope.

The end point was achieved in from 30 to 50 seconds in normal subjects. The time to end point in the abnormal group varied from 65 to 120 seconds.

It is significant that the rapidity of response in abnormal subjects was grossly proportional to the degree of obstruction evidenced clinically. For example, the uppermost curve in the abnormal group was that of a patient who had occlusion of the superficial femoral artery with sufficient collateral circulation to give him a palpable popliteal pulse. The lowermost curve was that of a postoperative femoral graft patient who, 1 year after operation, entered the hospital with acute occlusion of the graft and developed a white, pulseless limb. At the time of operation there was complete ischemia of the leg, as suggested by the lack of any response to the isotope test.

Fig. 5 depicts the pre- and postoperative response of the latter patient, who underwent a successful regrafting procedure and had return of the pedal pulses.

DISCUSSION

With the procedure described, a vascular space exists distal to the tourniquet which is free of radioactive material. This space has volume, V_t.

After the release of the tourniquet this volume (V) can be divided into 2 subvolumes, V_1 and V_2. V_1 equals that part of the original volume (V_t) that is filled with radioactive material. V_2 equals that part of the original volume (V) that is devoid of radioactive material. Thus, $V_1 + V_2 = V_t$ (equation 1). The blood containing radioactive material proceeds down the femoral artery and its branches until it reaches the aterioles. During this flow toward the arterioles no mixing need be postulated.

The release of blood from the arterioles into the capillary beds and subsequent collecting venules then occurs. The collecting

venules will now contain blood with radioactive material and also nontagged blood. Thus, the collecting venules will represent the radioactivity of the blood arriving at the arterioles mixing with the blood free of radioactivity. This mixing occurs because of the arteriolar sphincters which may retard emptying of some of the arterioles. It is at this collecting region that mixing occurs.

This assumed mechanism can be expressed as equation 2,

$$\frac{dV_2}{dt} = \frac{(F \times A)}{(Vt)} \times V_2 = -kV_2$$

where $k = \frac{F \times A}{V_t}$, F equals an equivalent flow in milliliters per area times time, A equals an equivalent area, and V_t equals total vascular volume of the limb. F and A are equivalent values and constants since the actual flow and cross sectional area change from point to point over the vascular tree.

The negative sign implies a continuing decrease in V_2 from time zero (the release of the tourniquet).

Integrating equation 2,

$$V_2 = V_2^{o}e^{-kt},$$

where $V_2^{o} = V_2$ at $t = O$, but at $t = O$, $V_2 = V_t$. Thus, equation 3 is

$$V_2 = V_t e^{-\frac{FA}{V_t}t}$$

But from equation 1 ($V_t = V_1 + V_2$), substituting equation 3,

$$V_t = V_1 + V_t e^{-\frac{FA}{V_t}t} \text{ or } V_1 = V_t\ (1 - e^{-kt})$$

The radioactivity is proportional to V_1

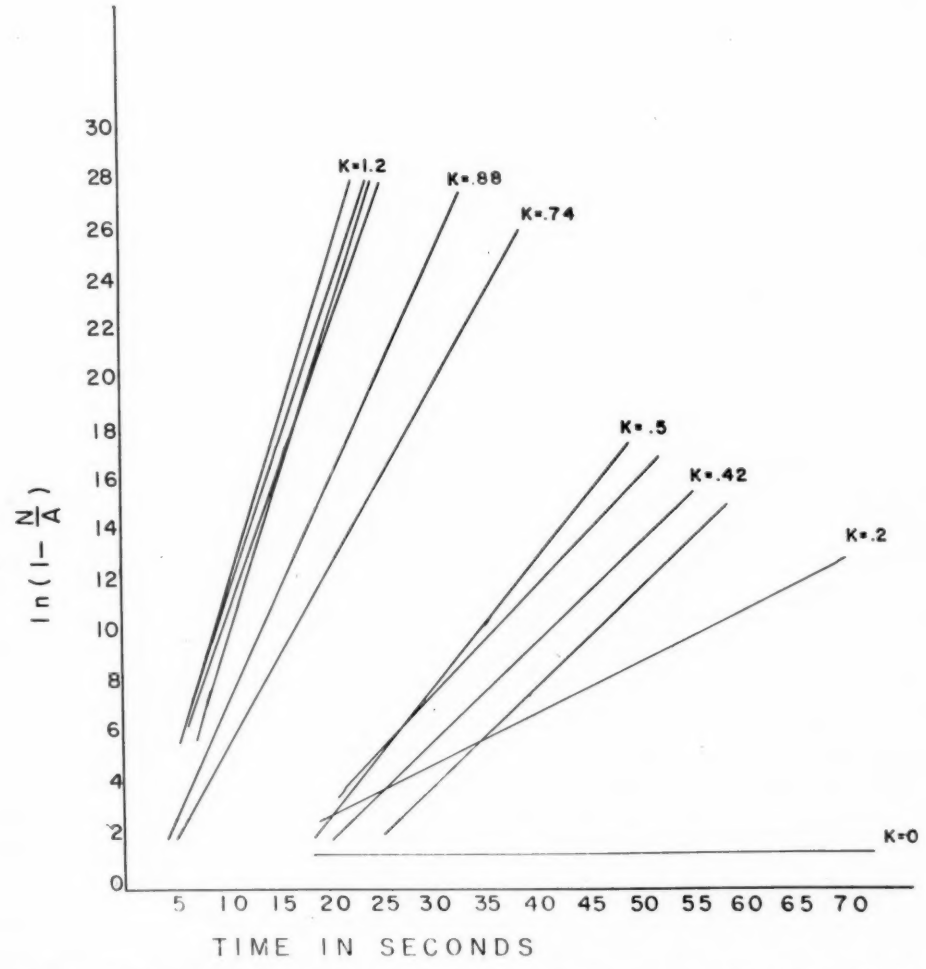

Fig. 6. Graph shows how k relates to the slope of the curves achieved by plotting $\ln\left(1-\frac{N}{A}\right)$ versus time. The slope, or k, decreases with disease. k values below 16 indicate arterial occlusive disease.

Table I

Age	*Signs and symptoms*	*k×10²*	*Relaxation time T (sec.)*	*Lag time (sec.)*
27	Control	7.4	13.5	3.0
39	Control	6.4	15.6	4.0
46	Control	8.0	12.5	3.5
51	Control	7.0	14.3	3.0
54	Control	7.0	12.2	2.0
56	Control	12.2	8.2	2.0
56	Control	11.5	8.7	2.0
60	Control	10.0	10.0	2.0
39	Iliac block	3.0	33.3	7.5
49	Femoral block	4.0	25.0	11.5
55	Femoral block	5.0	20	7.5
57	Femoral block	5.1	19.5	10.5
60	Femoral occlusion	4.0	25.0	7
61	Femoral occlusion	4.3	22.8	7.5
64	Midfemoral block	4.1	24.4	15
65	Femoral block	4.0	25.0	6
54	Complete graft occlusion	0	00	(No response)

and after a sufficient time has elapsed V_1 equals V_t. Thus, in equation 4,

$$N = A\ (1 - e^{-\frac{FA}{V_t}\ t})$$

where N equals radioactive counts at a time t and A equals maximum of radioactive counts achieved after complete filling.

Plotting N versus t, we get curves of the same shape as our experimentally derived response curves, which verifies our assumption as to the mechanics of flow, at least to the first order approximation.

The constant $k - \frac{FA}{V_t}$, as previously mentioned, thus depends on flow, crossectional area, and the vascular volume V_t. The flow is dependent on a number of variables, the most important being tube diameter, blood pressure, elasticity of the arterial and arteriolar system, viscosity of the blood, and the pulsatile character of the blood flow. Of these parameters, tube diameter is the primary determination of F, since the resistance to flow varies inversely with the fourth power of the tube radius. It seems, therefore, that the value of the parameter $\frac{FA}{V_t} = k$ should correlate well with the presence and degree of narrowing and obstruction resulting from arterial occlusive disease.

$\frac{FA}{V_t}$ has the dimension of reciprocal seconds and is the reciprocal of the relaxation time T ($T = \frac{V_t}{FA}$).

T represents the relaxation time of the filling process which is the time necessary for the radioactive material to wash in to 1/e of the total volume V_t.

Plotting $\ln\ (1 - \frac{N}{A}$ versus time in seconds), a series of straight lines results, the slope of which is the disease constant $k = \frac{FA}{V_t}$. For convenience we have plotted log base 10 and T represents the time needed to fill 1/10 of the volume V_t with radioactive material.

These curves exhibit 3 features, at first a lag time, then a straight-line portion, and at the end an upward deviation from the straight line.

Table I summarizes the experimental results. The plots on patients with known arterial disease gave very good straight lines after an initial lag period. On controls, the best straight line through a set of points was chosen. It is possible that the more rigid arterial walls of the experimental patients gave rise to less nonlinear flow effects than the elastic arterial walls of the control group.

SUMMARY

A method in which radioactive iodinated serum albumin is utilized for the evaluation of the rate of blood flow in extremities has been presented. The reliability of the method was tested in the laboratory on animals and substantiated by mathematical analysis. The efficiency of the method is undeniable and it is safe. The dosage of the tracer used is less than that used for a thyroid uptake test.

Use of the mathematical expression of the curve allows the examiner to plot the results in such a manner that previous annoying sources of error are automatically corrected and a numerical index of flow

is achieved. Use of a numerical expression permits ready recognition of diminished flow in a simple standard manner and provides a base line that can be re-evaluated during the course of therapy.

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Venous occlusion of the terminal ileum: an experimental study

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The basic unit of the intestinal organ, the cell, should have prime consideration as pathologic processes impinge upon its normal function. The goal of this experimental study was to relate the alterations in the gross appearance of the dying intestinal cell to its oxygen tension and pH. In an effort to compile data on the oxygen tension and hydrogen ion concentration in the cellular environs, we studied a strangulated segment of terminal ileum viewed through a plastic abdominal window. It was hoped that a less artificial environment for study of venous occlusion might be obtained with the use of the abdominal window.

This paper represents a study of venous occlusion in an apparently closed loop of terminal ileum in 10 dogs in which abdominal windows had been placed.

EXPERIMENTAL METHOD

Plastic window insertion. The technique for inserting a plastic window in the anterior abdominal wall of the dog has been previously described.[6] Two weeks were allowed before strangulation experiments were performed. Fourteen dogs had Plexiglas windows implanted in the abdominal wall, but 4 were excluded because of adhesions and infection. A screw tap was placed at one end of the plastic window so that studies could be carried out without removing the window (Figs. 1 and 2).

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Strangulation obstruction technique. With the animal under light Nembutal anesthesia (10 mg. per kilogram), a segment of ileum 30 cm. in length approximately 30 cm. from the ileocecal valve was chosen as the site of obstruction. The veins draining this segment were ligated. This portion of the terminal ileum was manipulated into a circular loop and a linen ligature was loosely applied so as not to prevent arterial inflow. The closed loop was returned to the peritoneal cavity via the screw opening in the Plexiglas window.

Methods of measuring oxygen tension. The apparatus was adapted from the tensiometer designed by Davies and Brink[3] and utilized by Montgomery and Horowitz[7-9] (Fig. 3). It consisted of a platinum electrode in a fixed low voltage. The resultant current was proportional to the oxygen tension in the cellular environment and could be read as deflections on a galvanometer.

Fluctuations in the oxygen tension attributable to temperature and precipitation of proteins on the electrode were minimized by utilization of a constant voltage of lv. and by reading the galvanometer 10 seconds after the application of the electrode to the bowel wall. A 60-second interval was allowed between readings and an average of 3 readings was recorded at any given time. The electrode pierced the gut wall for about 2 mm. at an angle of 60 degrees. Calibration of the electrode was obtained by determination of oxygen tension in nonviable bowel in saline solution of known oxygen tension. Corrections were made for temperature.

In order to demonstrate that the oxygen tension measured was in the tissue, readings were taken from normal bowel and 60 minutes after arterial occlusion. If the arterial supply was restored and the animal was permitted to breathe 100 per cent oxygen, the segment improved remarkably in color in 30 seconds. However, the oxygen tension remained at a low level for approximately 120 seconds and then increased rapidly. This was construed as some evidence that the oxygen tension in the cells or interstitial fluid was being measured rather than the oxygen tension in the small peripheral vessels.

Method of measuring pH. A modification of the technique employed by Claff and Swenson[1] was used. A microglass electrode

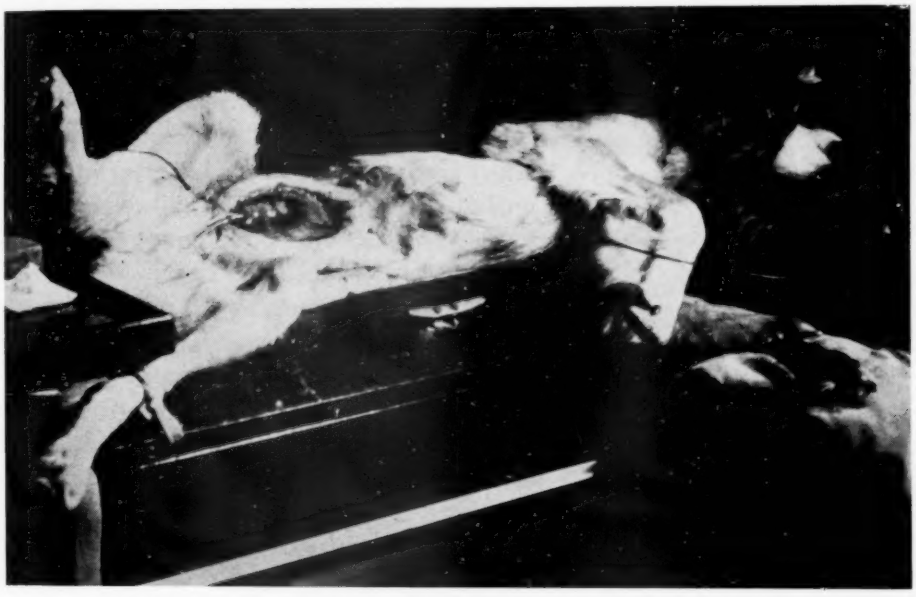

Fig. 1. Animal with Plexiglas abdominal window undergoing strangulation experiment under continuous light Nembutal anesthesia.

Fig. 2. Close-up view of abdominal window. Note the strangulated segment.

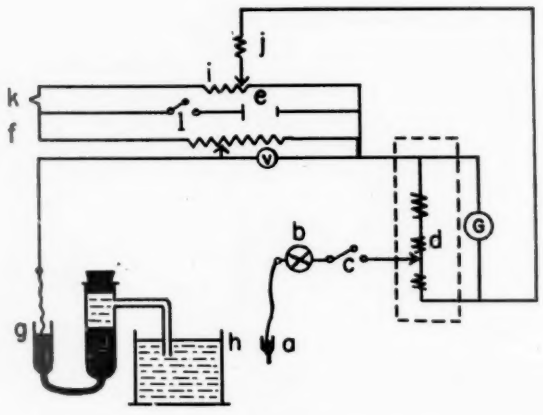

Fig. 3. Diagram of the circuit of the oxygen tensiometer. *a*, Electrode tip (cathode); *b*, selector switch; *c*, electrode switch; *d*, Aryton shunt resistance to 65,000 ohms; *e*, dry cell (1.5 v.); *f*, variable resistance; *g*, calomel half cell (anode); *h*, 0.85 per cent sodium chloride in beaker; *i*, variable resistance (500 ohms); *j*, fixed resistance (2 million ohms); *k*, fixed resistance (40,000 ohms); and *l*, main switch. *G*, Rubicon galvanometer, and *V*, voltmeter. The circuit is completed after the insertion of the animal's tongue in the beaker of saline solution and the electrode in the bowel wall.

which required as little as 0.05 ml. of fluid was used for determination of the hydrogen ion cencentration (Fig. 4).

The microtube was inserted beneath the serosa for about 2 mm. at an angle of 60 degrees and allowed to fill by capillary attraction. The subsequent measurement of the electromotive force coincided with the technique of Claff and Swenson. Using a standard acetate reference buffer solution with a tolerance error ± 0.02, we recorded reproducible results within the tolerance of the buffer solution.

EXPERIMENTAL DATA

Gross appearance of bowel and mesentery.

Normal bowel. The mesentery was approximately 2 mm. thick, smooth, glistening, and pale pink. Mesenteric vessels coursed through it, producing vascular arcades. The bowel diameter was approximately 1.2 cm. and the bowel wall was 3 to 4 mm. in thickness. The serosal surface had a bluish pink hue. The antimesenteric border was irregular from peristaltic indentations. At least 4 types of movement could be discerned; pendular, constrictive, rotary, and long undulating waves. The degree of activity appeared to have a direct relationship to the height of the pulsations of the mesenteric arteries.

Thirty minutes after venous occlusion. The mesentery had doubled in thickness and appeared hemorrhagic with mottled areas of cyanosis. Arterial pulsations could be observed easily. The serosa was smooth, glistening, and moist. The diameter of the bowel was 1.75 cm. Constrictive and pendular types of peristalsis were present. The color of the bowel was red to pink with mottled areas of congestion. There were numerous transverse indentations which extended to the antimesenteric border of the bowel. Dilated mural vessels lay prominently in these grooves. The bowel looked as if it has been converted into thousands of tiny sphincters approximately 2 mm. apart.

One hour after venous occlusion. The mesenteric vessels lay in deep furrows at 2 to 6 cm. intervals. The mesentery looked like ballooned triangles with the bases nearest the gut wall. There was little change in the general appearance of the bowel wall except for mottled congestion.

Two hours after venous occlusion. The mesentery appeared to be overriding the intestine and dissecting the serosa from the longitudinal muscle layer. The mesentery was 1.5 cm. thick and looked spongy, wet, and granular. The diameter of the intestine was 2.25 cm. Infinitesimal trauma to the intestinal wall which produced spasm caused occlusion of the bowel lumen. Small spastic areas appeared as pasty, bluish-white depressions. Some of the capillaries had ruptured and gave the gut a flea-bitten appearance. The intestinal wall had increased to 0.55 cm. in thickness. Arterial pulsations could be seen. The most pronounced change remained in the mesentery.

Three to 5 hours after venous occlusion. The mesentery had shortened and produced a peristalsis-like effect. Dissection of the serosa continued. More fibrin had accumulated on the surface of the gut and mesentery. Not infrequently a capillary bed with

all its arborizations could be made out with small knobs which represented rupture of the limbs of the capillary tree. The antimesenteric border was irregular and looked cyanotic. The diameter of the gut was 2.4 cm. The arterial pulsations were no longer visible.

Five to 8 hours after venous occlusion. The mesentery had increased to 2.2 cm. in thickness. The mesenteric triangles were adherent from the deposition of fibrin. It seemed that there was little transudation of fluid into the peritoneal cavity, but that the fluid was sequestered in the layers of the bowel wall. The diameter of the bowel had increased to 2.6 cm. There were numerous cyanotic areas that contained hematomas of dark black blood. The mural veins had formed straight, dilated lines accentuated by dark blood. Pendular peristalsis was present.

Eight to 12 hours after venous occlusion. The mesentery was 2.4 cm. in thickness and was very granular. Dissection of the serosa had ceased due to the disproportionate increase in the gut wall. The bowel had a reddish-blue tinge. The hematomas were numerous and were becoming confluent. In areas along the antimesenteric border, some of the hematomas had ruptured and left large drops of black, incoagulable fluid on the serosal surface. Thromboses were prominent in the vasa recta and the arcuate vessels. Merely touching the serosa would cause it to break. The bowel wall had thickened to 0.85 cm. Temperature had declined from 38° to 27° C. No peristalsis was evident.

Twelve to 15 hours after venous occlusion. The condition of the mesentery was unchanged. The bowel had a bluish-black color with a granular feel. The antimesenteric border was bathed in a black, incoagulable fluid from the herniated hematomas. The line of demarcation between the strangulated loop and the bowel above and below was quite striking. Cyanosis was most pronounced as transverse streaks leading into the mesenteric furrows. The mesentery was 2.5 cm. thick. The diameter of the intestine was 2.8 cm. and the gut wall was 1.4 cm. in thickness. The entire loop had a diffusely black color. The gut wall was smooth and motionless at this stage.

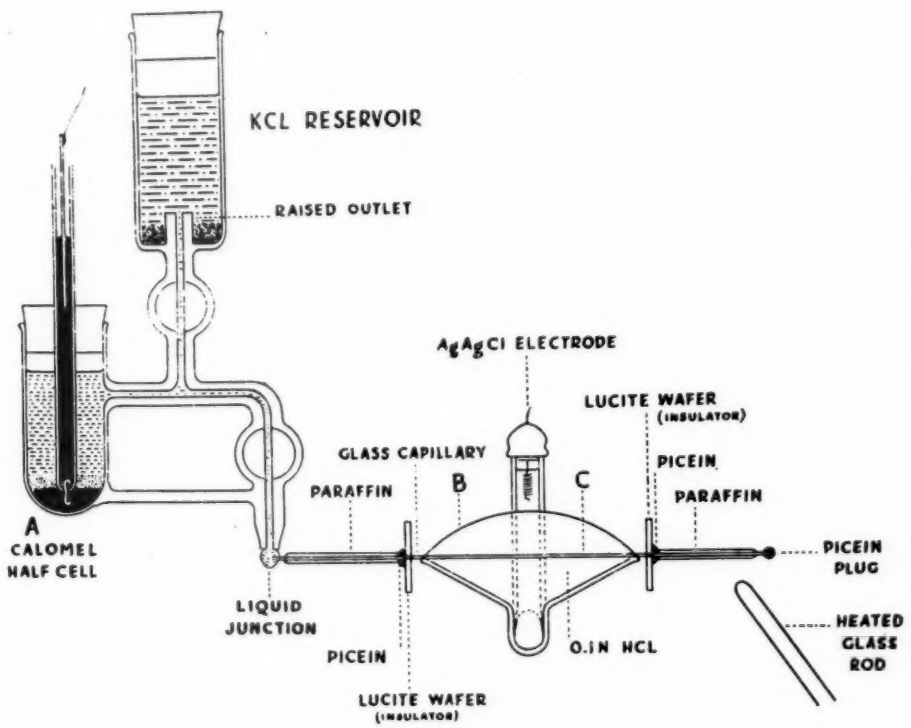

Fig. 4. Diagram of pH meter.

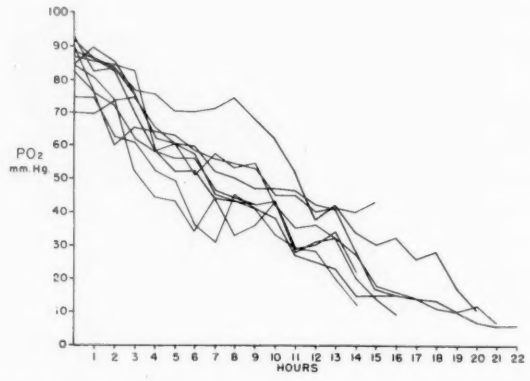

Fig. 5. Alterations in oxygen tension in 10 dogs with venous occlusion of 1 foot of terminal ileum.

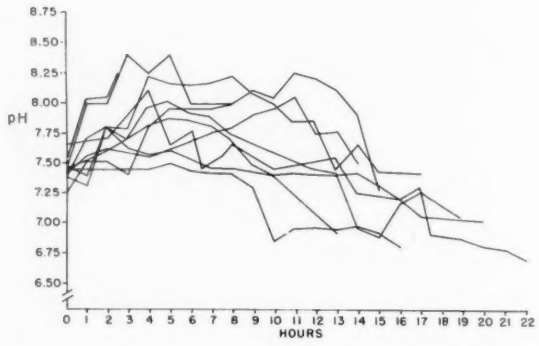

Fig. 6. Changes in pH recorded in 10 dogs after venous occlusion of 1 foot of terminal ileum.

Fifteen to 20 hours after venous occlusion. No visible changes in the bowel could be recorded from this point.

Peritoneal fluid. During the experiment 35 to 160 ml. of transudate was collected. The weight of the bowel at the time of death had increased an average of 301 per cent. Initially the fluid was clear, serous, and odorless. Between 6 and 12 hours the fluid had become incoagulable and had the odor of decaying blood. After the fourteenth hour the fluid had become thick and dark red to black in color. With the window technique it was impossible to calculate fluid loss from peritoneal absorption or dilution.

DISCUSSION

In this series of experiments the greatest decrease in oxygen tension was between 2 and 12 hours (Fig. 5). The measurement of oxygen tension in the cells declined as time after occlusion increased but the cells appeared to utilize oxygen for 18 to 20 hours. It may be that further oxygen utilization represented bacterial metabolism rather than consumption by the intestinal cells. However, the fact that the oxygen tension in the dying tissue was not equal to the oxygen tension of the air would indicate that some type of cellular activity persisted. In spite of continuing cellular respiration, numerous thromboses in the mural vessels and vasa recta made it impossible to restore normal oxygen consumption after 18 to 20 hours. Even if thromboses were not present, the edema and hemorrhage into the bowel wall, no doubt, would preclude adequate oxygenation.

Rising intercellular pressure as evinced by the gradual increase in size and weight of the bowel wall probably also contributed to the reduction in the diffusion gradient of oxygen to the cells. Intercellular pressure must be equal to the arterial inflow pressure at the end of 14 to 16 hours of obstruction, for there was no detectable increase in the weight of the bowel and mesentery after that time interval. Additional studies will be required to relate intercellular pressure to oxygen tension and pH.

There was an alkaline pH in the period of greatest oxygen decline (Fig. 6). As bowel ischemia increased, cellular autolysis began. Oxygen deprivation and changing pH may alter the structure of the cell membrane and make it more permeable. With a postulated increase in cell membrane permeability, there could be an ingress of alkaline salts from the blood into the interior of the cell.[5, 10] This mechanism may account for the paradoxical alkalinity which occurred between the second and fourteenth hours after venous occlusion. The cellular environment is in reality acidic, but this is masked by the collection of alkaline fluids.

The physical appearance of the bowel after 12 to 14 hours of venous occlusion in a closed loop had a fairly accurate biochemical correlation. After 12 hours, there was no motility of the diffusely black and edematous bowel. There were herniated hematomas on

the antimesenteric border. The serosa broke upon gentle touch, the temperature had declined 9° C., and the bowel wall had become sausage-shaped and approximately twice its original thickness. There was much variation, but it appears that the point of irreversible necrosis is reached when the serosa will break upon touch, the bowel wall has increased to twice its thickness when compared with the normal bowel below the strangulation, and the temperature has decreased 8 to 10° C. After a 12- to 14-hour period of venous strangulation, there was a critical decline in oxygen tension and evidence of rising hydrogen ion concentration.

The average length of survival of the 10 dogs after venous ligation in an apparently closed loop of a 1-foot segment of terminal ileum was 13.4 hours.

It is not to be inferred that these observations are necessarily basic. Rather, they tend to confirm and amplify the conclusions of previous investigators.

SUMMARY AND CONCLUSIONS

1. An attempt was made in 10 dogs to correlate oxygen tension and pH changes with gross appearance in a hypoxic segment of terminal ileum.

2. The greatest decline in oxygen tension occurred in a 10-hour period between 2 to 12 hours after venous occlusion.

3. Acidic pH was recorded after 14 hours of venous obstruction but it is believed that an ingress of alkaline body fluids masked the true degree of cellular autolysis in the early hours of venous occlusion.

4. The point of irreversible necrosis in this series of experiments occurred after 14 hours of venous ligation and was grossly reflected in rupture of the serosa, increase in the bowel wall to twice its original thickness, and temperature decline from 38° to 27° C. The gross changes in hemorrhagic infarction closely paralleled declining oxygen tension and pH.

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Renal tubular necrosis: its relation to norepinephrine administration

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Nephropathies characterized by tubular lesions have been ascribed to a number of etiologic factors—burns, blackwater fever, transfusions with incompatible blood, sulfonamide intoxication, toxemias of pregnancy, uteroplacental damage, mercury poisoning, severe trauma, and shock.[4] Recently Boughton and Sommers[1] have described patients who at autopsy were found to have massive necrosis of the renal tubules and attributed the lesion to a combination of shock and administration of levarterenol, a vasopressor amine. Moyer and associates,[7] however, have reported that in the normotensive subject norepinephrine causes reduction of renal blood flow because of vasoconstriction, but in the hypotensive subject it markedly improves function. In view of the widespread usage of vasopressor agents in combating surgical shock, the question of possible renal complications is of more than mere academic interest. The present communication is a preliminary report of 11 instances in which renal lesions identical to those described by Boughton and Sommers were found at autopsy. The possible pathogenetic mechanism is discussed with regard to the alleged effects of vasopressor amines in normotensive and hypotensive states.

MATERIAL AND RESULTS

The patients studied represented a variety of surgical conditions (Table I). With the exception of those in Cases 1 and 5, all underwent either emergency exploratory operation of the abdomen or an elective procedure. Norepinephrine* administration in 5 per cent glucose infusions was instituted in the postoperative period immediately upon recognition of a state of peripheral circulatory collapse. The time interval between diagnosis of circulatory collapse and norepinephrine administration did not exceed a maximum of 1 hour. The dosage rate was varied in each case so as to restore and maintain normal blood pressure. In the majority of cases the patients died suddenly not long after termination of norepinephrine administration.

Necropsy was performed, on the average, within 8 hours after death. Nonprotein nitrogen was determined on blood obtained at autopsy.

Grossly, the kidneys were in no way remarkable. Microscopically, the renal lesion was quite distinctive and fairly uniform in all the patients. The intact glomeruli and the loops of Henle in the cortex stood out in marked contrast against a background of deeply eosinophilic, structureless tubules (Figs. 1 and 2).

The glomeruli were swollen and usually occupied the entire Bowman's space. Cellularity was not increased (Fig. 3). Along the rim between the swollen glomeruli and the capsule occasional desquamated epithelial cells and scanty amounts of proteinous ma-

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*Levarterenol hydrotartarate (Spofa).

terial were found. This was often but not invariably the case. The epithelium of Henle's loop appeared to be slightly swollen, but aside from this no abnormality could be seen either in nuclear or cytoplasmic structure. Very rarely small amounts of proteinous material were seen in their lumina.

Both the proximal and distal segments of the convoluted tubules were necrotic and showed complete dissolution of nuclei. The cytoplasm was coarsely granular and projected into the tubular lumina, either partially or completely occluding them. The interstitial spaces around the tubules were somewhat edematous, but free of inflammatory cells. The basal membrane was undamaged. In a few instances it was not discernible in the most severely damaged areas.

The medulla presented no pathologic changes. Casts were often found but were considered nonspecific and incidental.

In patients who underwent bile tract operations the liver was always examined in order to exclude possible hepatorenal syndromes, the pathogenesis of which is still obscure and not properly a part of the present study.

Appraisal of the severity of the tubular necrosis with regard to the total dose or the dosage rate of norepinephrine administration did not show any particular relationship. Neither did the nonprotein nitrogen bear any relationship to the amount of norepinephrine.

DISCUSSION

There are 2 generally accepted causes of tubular necrosis. One is toxins, either bacterial or chemical, and does not concern

Table I. *Patients with renal tubular necrosis who received norepinephrine*

Case No.	*Age*	*Sex*	*Diagnosis*	*Operation*	*Total dose (mg.)*	*Duration (hr.)*	*μg/hr.*	*Nonprotein nitrogen**
1	63	F	Pyosalpinx with generalized peritonitis†	None	6	48	125	73
2	31	F	Sigmoid cancer	Sigmoidectomy	20	10	2,000	146
3	51	M	Internal abdominal injuries	Laparotomy, suture of ruptured intestinal loops	15	8	1,880	216
4	38	M	Pelvic fracture	Laparotomy	40	72	550	200
5	24	M	Ruptured appendix with generalized peritonitis†	None	10	9	1,100	185
6	47	F	Choledocholithiasis	Choledocholithotomy	6	2	3,000	200
7	47	F	Bronchiectasis	Lobectomy	14	4	3,500	160
8	65	F	Choledocholithiasis	Choledocholithotomy, cholecystectomy	32	18	1,777	155
9	61	M	Hemorrhagic pancreatitis	Laparotomy	40	27	1,481	174
10	51	F	Ruptured appendix with generalized peritonitis	Appendectomy	22	18	1,222	180
11	68	M	Carcinoma ventriculi	Gastrectomy	24	14	1,714	163

*Postmortem.

†Clinically undiagnosed.

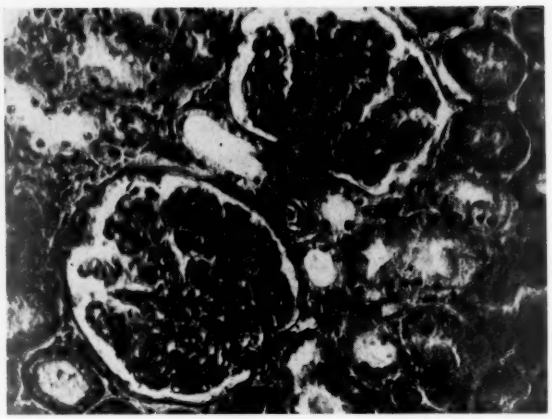

Fig. 1. Normal kidney. (Hematoxylin and eosin; ×170.)

us in this discussion. The other is ischemia. In spite of the number of excellent studies[5, 8] on tubular necrosis, it is still far from clear how ischemia acts in producing a selective necrosis of the convoluted tubules. The glomeruli, the loops of Henle, and the collecting ducts are known to be notably resistant to ischemia.

It is perhaps appropriate at this point to recall briefly the vasculature of the kidney. The renal artery, upon entry into the kidney, gives rise to the arcuate branch which courses between the cortex and the medulla. The interlobular artery passes off from the arcuate and traverses the cortex, sending the short vasa afferentia to the glomeruli. Beyond the glomeruli the vasa efferentia divides into 2 channels, one going to the peritubular network and the other (rectae) to the medulla (presumably in close association with the ascending and descending loops of Henle). The important point is that blood supplying the convoluted tubules and the medulla is, for all practical purposes, postglomerular in origin. The paraglomerular contribution is negligible, if at all operative. If ischemia intervenes, it is curious, then, why one segment, the proximal and distal tubule, should be injured while the other, Henle's loop and the collecting duct, remains intact.

Two problems arise, first, to explain how ischemia in general causes selective tubular necrosis, and, second, to explain how norepinephrine acts in producing the same type of lesion.

With regard to the first question, the usual explanation advanced is that the tubular epithelium represents a highly differentiated structure and hence is more vulnerable to ischemic injury than other segments of the nephron.[11] This concept was perhaps tenable at one time when the collecting ducts were considered merely inert conduits without functional significance. Today it is clear that, on the contrary, the ducts are highly specialized structures. In the countercurrent multiplier system proposed by Wirz,[13] it is precisely in the ducts that the glomerular filtrate is concentrated for final disposal, a process which requires an eminently high degree of differentiation.

A more plausible explanation for the genesis of tubular necrosis is to found in the new theory of plasma skimming in the renal vessels. It was originally proposed by Pappenheimer and Kinter[2, 3, 9] to provide a better account of certain fundamental facts peculiar to renal physiology, that is, constancy of renal blood flow, glomerular filtration, and arteriovenous oxygen difference over a wide range of arterial pressure.

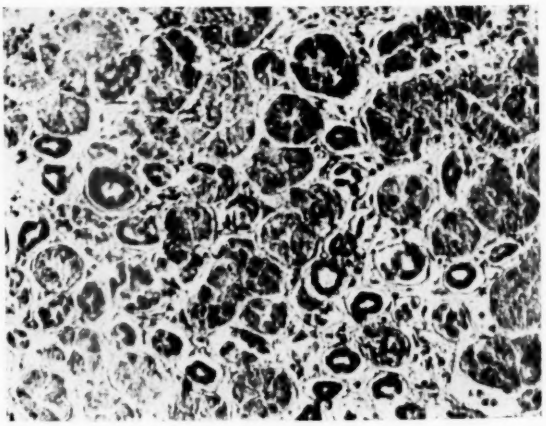

Fig. 2. Complete necrosis of the proximal and distal segments of the convoluted tubules with dissolution of structure and swelling of cytoplasmic remains. The dark structures interspersed among the necrotic tubules are the intact loops of Henle. The interstitial tissue shows moderate edema. (Hematoxylin and eosin; ×170.)

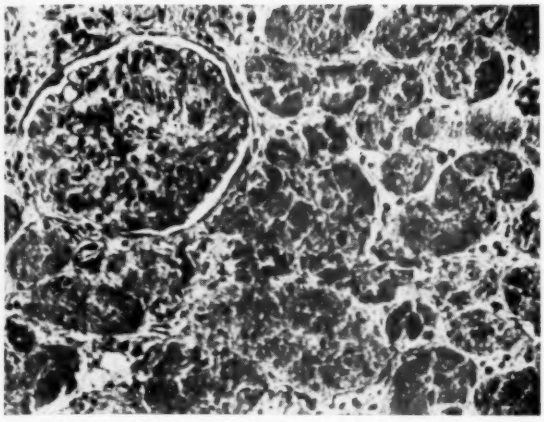

Fig. 3. Granular eosinophilic masses of necrotic tubular epithelium surrounding a swollen but otherwise intact glomerulus. Compare with Fig. 1. (Hematoxylin and eosin; ×170.)

The fundamental physical basis for this theory is a high velocity axial flow of red blood cells combined with branching networks which drain off plasma from the periphery of the flow stream. The degree of separation is dependent on the corpuscular content and the kinetic energy. With normal corpuscular content there is with each increment in arterial pressure a greater separation of blood into 2 streams. The net effect is increased vascular resistance due to increased viscosity, since the latter increases as a function of the third power of the red blood cell concentration. Such a mechanism would maintain renal blood flow and glomerular filtration at relatively constant rates regardless of wide arterial pressure fluctuations. In addition, shunting of the cell-poor moiety into the peritubular capillary system would imply a lower oxygen uptake from the blood stream and thus a low arteriovenous oxygen difference.

The critical assumption in the theory is a peculiar geometry of the renal vessels at 2 points. It is assumed that the afferent arterioles and the arteriole to the peritubular network branch off from their respective vessels at right angles so as to drain off the plasma much more effectively as the blood stream is separated.

Let us consider now how cell separation can produce selective ischemia of the tubules and necrosis. At a renal arterial pressure of 140 mm. Hg and a normal hematocrit of 0.45, the intrarenal hematocrit is 0.20. (The intrarenal hematocrit is one of the important points which demonstrate a redistribution of red blood cells and plasma in the kidney tissue.) Let us assume that for each 100 ml. of blood flowing through the kidney, 8 ml. of cells and 48 ml. of plasma pass through the tubules. This gives an intrarenal hematocrit of 0.14, which is fairly close to the value experimentally determined by Pappenheimer and Kinter and which indicates that most of the intrarenal hematocrit is contributed by the peritubular blood. The 8 ml. of erythrocytes bathing the tubules provides 3.5 ml. of oxygen. The rectae, on the other hand, contain 37 ml. of erythrocytes capable of delivering 16.1 ml. of oxygen to Henle's loop and the collecting ducts. Consequently, there is, under physiologic conditions, an uneven supply of oxygen to the nephron.

Let us now assume that there is a 60 per cent reduction in renal blood flow, due either to blood loss or internal redistribution of total blood, with roughly normal corpuscular content. Further, let us assume that shock is still in its reversible phase and that the renal arterial pressure is reduced to about 96 mm. Hg. This would mean that such a reduction in kinetic energy, with normal corpuscular content, would, as a first approximation, produce an intrarenal hematocrit of 0.28, or a reduction in cell separation by a factor of 1.4. The cell separation would still be of such a magnitude as to make the effect of decreased oxygen supply always much more severely felt in the convoluted tubules than in the loops of Henle and the collecting ducts.

It is probably the peculiar anatomic arrangement and the functional mechanism of cell separation which make the tubular epithelium more susceptible to ischemic damage than other parts of the nephron. The kidneys hence possess an intrinsic mechanism which, although admirably effective under a variety of conditions, can in certain circumstances be to their own detriment.

Table II. *Tubular sodium loss in hypotensive patients after norepinephrine administration (calculated from data of Moyer[7])*

Patient	*Glomerular filtration rate (inulin)*		*Plasma Na (mEq./L.)*	*Filtered Na load* (mEq./L.)*	*Excreted Na (mEq./min.)*	*% excreted Na lost through tubules**
W. H.	C	3	130	0.39	8	95
	V_1	114	128	14.5	20	27
	V_2	92	128	11.8	19	38
	B_1	67	133	8.9	25	64
	B_2	155	134	20.7	451	95
M. C.	C	10	135	1.4	39	96
	V_1	60	127	7.6	179	96
	V_2	78	127	9.9	192	95
	B_1	82	123	10.0	188	94
L. M.	C	—	135	—	0	—
	V_1	5	135	0.7	61	99
	V_2	16	131	2.1	152	98
	B_1	23	125	2.8	663	99
	B_2	119	123	14.6	108	87
T. H.	C	128	136	17.5	124	85
	V_1	137	135	18.5	114	84
	V_2	140	135	18.9	129	85
	B_1	184	136	25.0	276	91

*Calculated.

C, Control during shock.

V_1, Partial restoration of blood pressure with a vaso-pressor agent.

V_2, Complete restoration of blood pressure with a vasso-pressor agent.

B_1, Immediately after transfusion of blood.

B_2, Follow-up study.

It is believed that the illustration given provides a fairly good account of the genesis of tubular ischemia and necrosis. This is not to be construed that in its present form the theory does not raise a number of problems which still remain to be investigated. It does, however, offer a unifying concept, the predictions of which are amenable to experimental verification.

With regard to the effect of norepinephrine, it has been reported by Moyer and colleagues[7] that in the hypotensive state there is an improvement in renal function and blood flow. They suggest that the improvement is due to the ambivalent behavior of norepinephrine which causes differential vasoconstriction between the kidney and the remainder of the general circulatory bed. A re-evaluation of their data shows that their conclusions are completely untenable. First, analysis of the relationship between sodium excretion and urine flow shows an abnormally exaggerated osmotic diuresis, indicating impairment of tubular function. Furthermore, all of the filtered sodium was lost in the urine with no tubular reabsorption. Indeed, practically all of the urinary sodium was derived from nonfiltered sources, that is, tubular sources (Table II). This in itself is clear evidence of tubular dysfunction, if not frank necrosis. Consequently, it cannot be accepted as proved that norepinephrine has a beneficial effect on renal function as Moyer claims. In fact, the evidence is to the contrary.

Norepinephrine reduces renal blood flow by vasoconstriction.[10] Assuming that cell separation is in operation, the net effect would be the same as described previously, that is, deprivation of oxygen to the convoluted tubules first and foremost. If this vasoconstriction takes place under circumstances of a pre-existing reduction in renal blood flow such as in hypotension, the ischemic effect would be additive. Boughton and Sommers[1] originally implicated the combination of shock and norepinephrine as the cause of tubular necrosis in their patients.

But they were unable to explain the pathogenetic mechanism.

Additional evidence that vasopressor amines can produce tubular necrosis comes from experimental studies with serotonin (5-hydroxytryptamine). This substance, which is allied to norepinephrine in its vasoconstrictive properties, has been shown to be capable of producing renal necrosis and both tubular and massive cortical necrosis.[6, 12]

We have been impressed by the fact that a number of patients receiving equal or greater doses of norepinephrine than in the present series failed to show any morphologic signs of tubular necrosis. It appears that this may be due to either extreme hypotension or extreme vasoconstriction (physiologic or pharmacologic). These are the 2 conditions under which cell separation no longer operates in the renal vessels. In extreme hypotension (below a critical level) the kinetic energy available is insufficient to divide the blood into 2 streams. Similarly, extreme vasoconstriction reduces the velocity of blood flow to such a degree that axial streaming no longer obtains. In either case the normal unequal oxygen distribution would be nullified in order to compensate for a decrease in over-all oxygen supply. In effect, this would represent a check mechanism for extreme variations detrimental to renal function.

The importance of possible deleterious effects of norepinephrine administration lies perhaps not so much in the production of frank tubular necrosis as in the development of various degrees of tubular dysfunction. The latter is probably much more common than is suspected and, unless the clinician bears it in mind, can easily go unnoticed. This does not mean that it is of no significance. In the postoperative period, when the proper functioning of the body's homeostatic mechanisms is of the utmost importance, any unbalancing of homeostasis such as in tubular dysfunction with consequent loss of base conservation, to mention but one aspect, would prolong recovery and impair wound healing.

SUMMARY

A preliminary report of studies now in progress is presented on the effect of norepinephrine on the kidneys. It describes the postmortem finding of massive necrosis of the convoluted tubules with sparing of the glomeruli, the loops of Henle, and the collecting ducts. The lesion is attributed to the administration of norepinephrine. The pathogenesis of the lesion is discussed and is based on considerations of the theory of cell separation in the renal vessels.

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Mannitolization. I. The prevention and therapy of oliguria associated with cross-clamping of the abdominal aorta

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Cross-clamping of the abdominal aorta (CCAA) is necessary during abdominal aneurysmectomy. Many satisfactory operative procedures are complicated by oliguria, acute renal failure, and death. Powers[10] reported a 30 per cent incidence of oliguria and 4 fatal cases of acute renal failure which occurred after CCAA in a 12-month interval at Albany Hospital. Twenty per cent of the deaths associated with elective aneurysmectomy at the Mayo Clinic[12] are due to acute renal failure. Recovery from acute renal failure which complicates cross-clamping of the abdominal aorta is a rarity.

The lengthening life span and technical surgical advances increase yearly the number of elderly, poor-risk patients acceptable for aneurysmectomy and requiring CCAA. Therefore, the development of a safe method which protects against CCAA oliguria and acute renal failure is urgent and important. The only previously reported method requires the use of ganglionic blocking agents to maintain the systolic blood pressure at 70 to 80 mm. Hg during the operation.[10] The maintenance of hypotension in these elderly patients might increase the risk of cerebrovascular accidents and myocardial infarctions. Therefore, a more innocuous therapy is needed.

Studies at Walter Reed Army Medical Center in which dogs were utilized have shown that an abrupt decrease in renal blood flow, glomerular filtration rate, and urinary flow occurs when CCAA is performed.[6] One of the authors (A. C.) has found a similar abrupt fall in urinary flow in man when the aortic clamp is applied during aneurysmectomy.[8] Mannitol has been utilized by the Walter Reed Army Medical Center group to protect against epinephrine-induced fatal renal failure in dogs.[7] Water loading alone was unsuccessful.

The authors have successfully used intravenous mannitolization for the prevention and therapy of CCAA oliguria in human beings. It is the authors' judgment that the urgent need for safe protection against acute renal failure complicating aneurysmectomy warrants publication of a preliminary report. It is hoped that many centers will give this innocuous therapy prompt clinical trial.

METHODS

Mannitol is a 6-carbon hexahydric alcohol. It is distributed in the extracellular fluids and freely filtered at the glomerulus. It is not reabsorbed from the renal tubules. It is inert and nontoxic.[5] Theoretically, as a result of the noted properties, and in our experience, mannitol is the most effective and least toxic renal osmotic solute available.

Mannitolization was used by one of the authors (K. G. B.) for therapy in refractory

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cardiac and cirrhotic fluid retention unresponsive to the usual spectrum of diuretic regimens. The excellent results led to its use in cases of acute left and right heart failure. The diuresis was prompt and massive with parallel clinical improvement within 2 hours of initiation of mannitolization.[1] Mannitolization was then tried in 1 patient with acute cerebral edema after an open-heart operation. Again, prompt diuresis was obtained. Many of the patients studied were in precarious cardiopulmonary condition because of combinations of myocardial, valvular, and coronary heart disease. In over 50 trials, no evidence of circulatory overload or other deleterious effect was found.

The initial use of intravenous mannitolization in CCAA occurred when Patient 1 manifested oliguria after aneurysmectomy. A 50 ml. ampule of 25 per cent mannitol was heated to dissolve all crystals and aspirated into a preheated syringe. It was administered at approximately body temperature directly intravenously over a 3-minute period. The same procedure was followed in Patient 2. Since the therapy was effective in these oliguric patients, it was decided to try mannitolization prophylactically to prevent oliguria during CCAA. This was successfully accomplished in Patients 3 and 4.

An infusion of 5 per cent mannitol in water was initiated in Patient 3 after intubation, bladder catheterization, and urinary collection during a control period. An infusion rate of 10 ml. per minute was used until vigorous diuresis was established and then infusion flow rate was adjusted to maintain urinary flow rate every 10 minutes. During the period of CCAA a 20 per cent infusion at a maintenance flow rate was used. Paraamino-hippurate clearance was used to measure effective renal plasma flow; glomerular filtration was measured by insulin and endogenous creatinine clearance studies. The results are described in Case 3. The treatment of Patient 4 was performed as an emergency when our supply of mannitol was limited. Therefore, a smaller amount of mannitol was administered and administration was interrupted for 82 minutes. The experience with these 2 cases, especially the finding that effective renal plasma flow and glomerular filtration rate decreased abruptly when the aorta was clamped despite continuing diuresis (Case 1) prompts us to propose the following protocol:

1. oral water load, 20 ml. per kilogram, 0500 hours, day of operation
2. 0 to 10 minute control urine collection after intubation and urinary bladder catheterization
3. 10 minutes to approximately 45 minutes prior to clamp application, 5 per cent mannitol at 15 ml. per minute until urine flow stable for 10 minutes; then adjustment of infusion rate to equal urinary flow rate
4. 45 minutes prior to clamping, 20 per cent mannitol infusion rate adjusted to equal urinary flow rate
5. clamp application to abdominal closure; 5 per cent mannitol infusion adjusted to equal urinary flow

N.B. Infusion of 20 per cent mannitol for at least 30 minutes prior to cross-clamping takes priority over all other steps.

CASE REPORTS

Clinical study in postclamping oliguria.

Case 1. A 73-year-old white woman underwent aortic cross-clamping for resection of aneurysm on April 15, 1960. The aorta was cross-clamped above the right renal artery for 13 minutes. Fig. 1 demonstrates the occurrence of oliguria with urinary output averaging 14 ml. per hour and urinary specific gravity dropping from 1.020 to 1.013 during the 30 hours prior to the intravenous administration of mannitol. After the administration of 12.5 Gm. of mannitol over a 5-minute period, urinary output increased dramatically to 125 ml. the third hour after administration. The rate of intravenous fluid administration was not increased until after diuresis had been established. Also, the urinary specific gravity had followed the course usually seen in early renal failure and the blood urea nitrogen had risen from a preoperative value of 13 mg. per 100 ml. to 25 mg. per 100 ml. The failure of the urinary specific gravity to rise after mannitol had been given suggests that the patient was not dehydrated at the time of administration, since it has been our experience in other studies that the dehydrated patient will have urinary specific gravities of approximately 1.035 after mannitol infusion.

Case 2. A 67-year-old white man underwent sigmoidal resection for carcinoma on April 20, 1960. At the time of operation an aortic aneurysm was discovered and removed. Cross-clamping of

the aorta below the renal arteries was necessary. During the first 10 postoperative hours, the hourly urinary output averaged 6.5 ml. with a specific gravity of 1.016 as illustrated in Fig. 2. After administration of 12.5 Gm. of mannitol intravenously over a 5-minute period, the output increased dramatically to 20 ml. within 1 hour and 50 ml. per hour by 3 hours. In contrast to Case 1, the urinary specific gravity rose to 1.024, which is more commensurate with normal hydration. Again, the rate of fluid administration was not increased until diuresis had been established.

Comment. These cases represent 2 instances in which a medical regimen for acute renal failure was considered. The patient in Case 1 was over 72 hours postoperative and showed the usual milestones of acute renal failure as measured in terms of adequate hydration, stable blood pressure, specific gravity of 1.013, and rising blood urea nitrogen associated with oliguria. The failure to increase urinary specific gravity after mannitol administration was also suggestive of normal or overhydration. It should be recalled that the therapy once recommended for early post-traumatic oliguria included rapid administration of dextrose and water. Subsequently, it was thought that any beneficial effect was simply in the restoration of circulating blood volume or rehydration. Recently, the use of osmotic diuretics for hemoglobinuria in burn patients has been recommended.[4, 11] The possibility that mannitol, via its osmotic diuretic and probable homeostatic effects on the kidneys, may be therapeutic in early severe oliguria must be investigated.

Mannitolization abolished consideration of an acute renal failure regimen in these cases and reassured the authors concerning the patient's renal status in management. The delivery of urine in large amounts to the specimen bottle is the most important consequence of mannitolization in these cases of oliguria.

Clinical studies in the prevention of oliguria after aortic cross-clamping.

Case 3. A 63-year-old white man without previous history of cardiovascular renal disease and normal results of studies relative to these systems was noted to have an abdominal aneurysm on physical examination prior to radiation therapy of a nasopharyngeal malignancy. An elective aneurysmectomy in which a bifurcation graft was utilized was performed May 17, 1960. The changes of urinary flow associated with the operative procedure and mannitolization are illustrated in Fig. 3. Mannitol was used as a 5 per cent solution except during the period of cross-clamping of the aorta. During this 58-minute interval, 20 per cent mannitol was infused. A urinary flow rate of over 6 ml. per minute was obtained prior to clamping. Urinary flow continued to rise over 7 ml. per minute during occlusion of the aorta. Vital signs remained stable and the patient excreted over 3,000 ml. of urine during the 24-hour period subsequent to operation. Postoperatively, the blood urea nitrogen, serum electrolytes, and urinalysis remained unremarkable. Urinary specific gravity varied from 1.010 to 1.028.

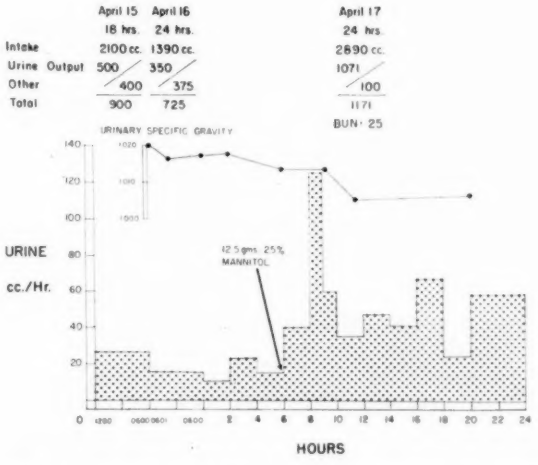

Fig. 1. Study of Case 1 was initiated at 1200 hours, April 15, upon admission to recovery ward after operation. Contiguous time intervals are plotted along the abscissa. The time scale is expanded on April 17 to emphasize the prompt diuresis after mannitolization. Arrow indicates initiation of a 3-minute mannitol infusion. Note drop in specific gravity from April 15 to 17. The further decrease during mannitol diuresis may indicate overhydration or intrinsic renal dysfunction.

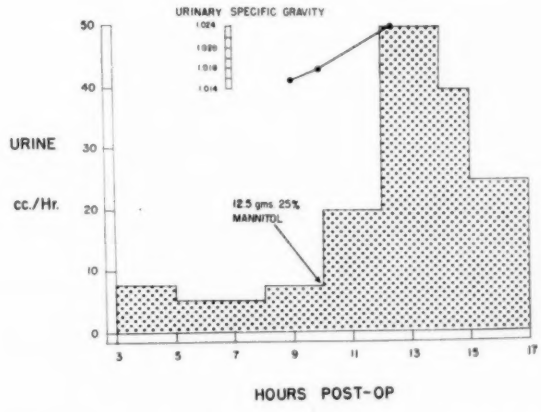

Fig. 2. Study of Case 2 was initiated 3 hours after operation. Note prompt diuresis after mannitolization. Arrow indicates time at which 3-minute mannitol infusion was started. Urinary specific gravity rose slightly during diuresis, possibly indicating normal hydration.

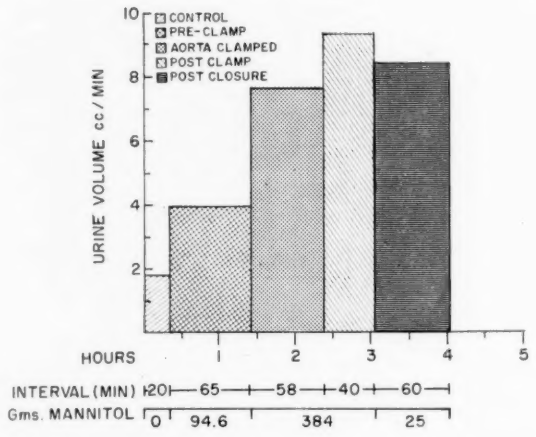

Fig. 3. Study of Case 3 was initiated after intubation and bladder catheterization. Time scale is contiguous. Control urine was collected prior to operation and postclosure specimens upon its completion. Below abscissa, concordant with time scale, are plotted time interval for each phase of the study and quantity of mannitol infused per interval. Five per cent mannitol was infused except during CCAA, when a 20 per cent solution was used. Note acceleration of urine flow which persisted through interval of aortic clamping.

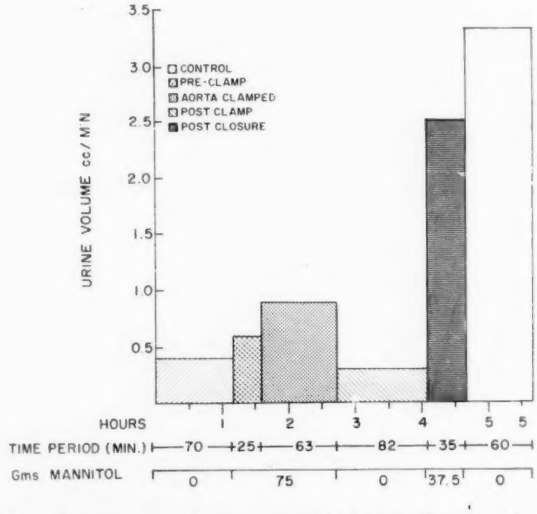

Fig. 4. Study of Case 4 was initiated after intubation and urinary bladder catheterization. The time scale is contiguous. Control urine was collected prior to operation and postclosure urine upon its completion. Below the abscissa concordant with the time scale are plotted the time interval for each phase of the study and the quantity of mannitol infused per interval. Mannitolization with a 15 per cent solution in water established an adequate urine flow during CCAA. Note the abrupt decrease of urine flow during the interruption of mannitol infusion and its dramatic increase upon resumption of the infusion.

Case 4. A 66-year-old white woman was admitted June 2, 1960, because of severe abdominal pain during the preceding 48 hours. A pulsatile abdominal mass was found and the diagnosis of abdominal aortic aneurysm with impending rupture was made. Pertinent history included hypertension of 20 years' duration, episodes of cerebral vascular encephalopathy in 1945 and 1955, anterior wall myocardial infarction followed by chronic congestive heart failure in 1956, and diabetes mellitus which had required hypoglycemic therapy since February, 1960. Physical examination showed a blood pressure of 180/100 and confirmed the impression of abdominal aneurysm. The blood urea nitrogen was 22, and albuminuria and pyuria were present. Emergency laparotomy showed an aortic aneurysm beginning just below the renal arteries and extending to the aortic bifurcation. A bifurcation graft was required. Fig. 4 illustrates the variation in urinary flow correlated with the surgical procedure and mannitolization. The control period followed intubation and bladder catheterization. The mannitol supply was limited, so 75 Gm. was administered as a 500 ml. infusion over an 88-minute period. The urine flow is not comparable to that in Case 3, probably because of the limited amount of mannitol and rate of infusion utilized. However, an adequate urinary flow was obtained and sustained throughout the 63-minute period of aortic cross-clamping. The diuresis obtained with mannitolization was highlighted by the fall in urinary flow to 0.3 ml. per minute during the 82-minute interval when the patient received no mannitol and the increase to 2.5 per minute promptly upon the reinstitution of a 15 per cent mannitol infusion as shown in period 5. During the 24 hours subsequent to operation, the urinary volume totaled 1,280 ml. Six days postoperatively the blood urea nitrogen was 23 mg. per cent and a random urinary specific gravity determination on an aglycosuric specimen was 1.020.

Comment. The use of prophylactic mannitolization in these 2 patients illustrates 2 important features. First, mannitol as used in these patients caused no observable toxicity. The patient in Case 4 had severe chronic cardiovascular disease with congestive heart failure and diabetes, but showed no evidence of overloading of the circulatory system during or after mannitolization. Second, mannitol produced a diuresis throughout aortic cross-clamping which cannot be obtained by simple water loading and which would be hazardous to attempt with other osmotic agents such as sodium chloride or hypertonic glucose.[3]

DISCUSSION

Oliguria and acute renal failure associated with cross-clamping of the aorta in

human beings is a dread and usually fatal complication. Vigorous programs in basic and clinical research into the mechanisms and prevention of acute renal failure are being actively pursued in many centers.[3, 6, 10, 12] When one of the authors (K. G. B.) found mannitol, a 6-carbon hexitol, effective and safe for use in diuretic therapy for refractory fluid retention, acute left ventricular failure, and cerebral edema, study of mannitolization in patients subjected to CCAA during aneurysmectomy was undertaken.[1]

Experimental studies have shown a marked decrease in renal blood flow, glomerular filtration rate, and urine flow associated with aortic cross-clamping below the renal arteries in animals.[6, 10] The performance of parallel studies in patients is not ideal or precise. However, studies at the Walter Reed Army Medical Center have shown a marked decrease in urine flow during and after aortic cross-clamping in the human being.[8] Patient 3 showed an increasing diuresis during cross-clamping despite abrupt decrease in renal plasma flow (CPAH) and glomerular filtration rate (C_I, C_{cr}). It is believed that mannitol prevented the expected associated decrease in urine flow.

Mannitol is freely filtered at the glomerulus and is not reabsorbed. The high osmotic activity of mannitol is thus concentrated throughout the tubular lumina. Increased renal fluid volume without significant change in general circulatory hemodynamics may occur. It has been shown by Bounous[3] and others that hypertonic glucose causes an increase in renal blood flow accompanied by an increase in cardiac output and circulating blood volume. Bounous believes that the changes in renal blood flow are related more to blood sugar levels than to change in cardiac output or blood volume. Mannitol has approximately the same particle size as glucose, but is limited to the extracellular space, is not reabsorbed from the renal tubules, and is not metabolized. Therefore, given in equivalent amounts, its renal osmotic effect should be more marked and of longer duration. We believe that this is the case. Therefore, mannitol held in the tubular lumen may cause an increase in fluid volume localized to the tubular lumen discouraging tubular collapse. There may be a local increase of nutrients necessary for renal tissue metabolism which protects the kidney during subsequent decreased renal blood flow caused by aortic cross-clamping. The protective effect of mannitol against experimental epinephrine renal shutdown[7] may operate through a similar mechanism.

Since a high concentration of mannitol in the tubular fluid is needed prior to clamping, it is recommended that 20 per cent mannitol be infused for 30 minutes prior to CCAA.

Experimental studies to elucidate the mechanism of mannitol protection against the renal effects of CCAA are planned.

SUMMARY

Cross-clamping of the abdominal aorta (CCAA) is regularly accompanied by oliguria. Acute renal failure is a serious and frequently fatal complication of CCAA.

This preliminary report is prompted by the dramatic effectiveness of intravenous mannitolization in overcoming oliguria after CCAA in 2 patients and in preventing oliguria during CCAA in 2 patients.

It is proposed that this safe and apparently successful technique for the prevention of CCAA oliguria be given clinical trial in other hospitals.

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Postoperative endocarditis due to Candida: clinical observations and the experimental production of the lesion

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Postoperative endocarditis is an infrequent but dreaded complication of operations for the correction of congenital or acquired heart disease.[2, 3] The rarity of the disease is somewhat surprising since all intracardiac procedures result in some damage to the endocardium and foreign bodies in the form of sutures or prosthetic materials are usually inserted. Although a certain number of microorganisms are probably introduced into the circulation in the course of every cardiac operation, the size of this inoculum can be minimized by vigilant asepsis and the defense mechanisms of the patient will ordinarily prevent the development of infection. Also, in many clinics, antibiotics are routinely administered during the early postoperative period, although the role of such prophylaxis in preventing postoperative endocarditis has not been established.

The most lethal form of postoperative endocarditis is that in which the responsible organism is a fungus.[7] Only 2 patients who developed postoperative fungal endocarditis have been described in the surgical literature[4, 6] and in each the disease was recognized only at autopsy. Three patients in this clinic have developed mycotic endocarditis after operations for rheumatic heart disease. Although the infections were recognized and treatment was undertaken, each patient died.

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This experience prompted an investigation of methods for the production of fungal endocarditis in experimental animals and of the factors which influence the development of the disease. In the present report, the results of these studies are presented as well as brief clinical descriptions of the patients in whom endocarditis occurred.

CASE REPORTS

Case 1. G. V., a 45-year-old man, had acute rheumatic fever at the age of 25 and symptoms of dyspnea and easy fatigability had been noted for several years before his admission. The clinical findings indicated the presence of mitral stenosis. This diagnosis was confirmed at cardiac catheterization when he was found to have a mean left atrial pressure of 22 mm. Hg and an end diastolic gradient of 15 mm. Hg across the mitral valve. In April, 1958, a closed mitral commissurotomy was performed. The valve leaflets were mobile and a satisfactory valve opening was accomplished by digital fracture of the commissures. The patient tolerated the operation well and the postoperative course was uneventful except for the development of atrial fibrillation which could not be converted with quinidine. He was given 1.0 Gm. of streptomycin and 1.2 million units of penicillin daily for 8 days postoperatively and penicillin orally for an additional week. The patient was discharged from the hospital 20 days after operation. Two weeks later he developed fever, sweating, and weakness which persisted in spite of treatment by his physician. When readmitted 9 weeks after operation he was found to have low grade fever and enlargement of the spleen. An apical systolic murmur, not present at the time of his discharge, was

audible. Blood cultures revealed a heavy growth of *Candida parakrusei*. In spite of intensive treatment with amphotericin B, the patient died 5 weeks after the presence of the infection had been proved. At autopsy active endocarditis which involved the mitral valve and left atrium was evident and *Candida* was cultured from the vegetations present. Microscopic sections of a vegetation on the anterior mitral leaflet demonstrated the presence of abundant moniliform organisms. Infarcts in the spleen, kidney, liver, lung, and hilar lymph nodes all contained the organism.

Case 2. M. S., a 39-year-old housewife, had had chorea at the age of 9 and an attack of acute rheumatic fever at the age of 29. Since the age of 34 she had experienced increasing cardiac disability. On clinical examination she was in evident cardiac failure and the murmurs of mitral stenosis and regurgitation were audible. At left-heart catheterization the mean left atrial pressure was 34 mm. Hg, an end diastolic gradient of 11 mm. Hg was recorded across the mitral valve, and the contour of the left atrial pressure pulse indicated gross mitral regurgitation. In November, 1958, an open surgical repair of the mitral valve was undertaken. During complete cardiopulmonary bypass, for a period of 1 hour, a posterior annuloplasty was performed and the anterior commissure opened. After operation the patient's course was smooth but her convalescence was slow. She was given 1.0 Gm. of streptomycin daily for 5 days, 1.2 million units of penicillin daily for 14 days and penicillin orally for an addioxygenator at the end of the perfusion grew only tional 16 days. A culture of blood taken from the a Flavobacterium which was thought to be a laboratory contaminant. The patient was discharged 4 weeks after operation. Three and one-half months after operation the patient was readmitted because of progressive cardiac failure and fever. *Candida guilliermondi* was grown from the blood in pure culture. Therapy with amphotericin B was initiated, but the patient died 2 weeks after treatment was begun. At autopsy 2 vegetations were present on the mitral valve and one on the right coronary cusp of the aortic valve. Cultures and microscopic sections of these vegetations showed them to be *Candida guilliermondi*. Embolic abscesses were found in the spleen, kidney, brain, and spinal cord.

Case 3. H. D., a 48-year-old dentist, presented with a history of rheumatic fever and the physical findings of aortic stenosis. Left-heart catheterization showed an elevated left atrial pressure, a left ventricular pressure of 250/40 mm. Hg, a brachial artery pressure of 130/70 mm. Hg, and a cardiac output of 6.4 L. per minute. The peak systolic gradient of 120 mm. Hg across the aortic valve indicated severe stenosis. Aortic valvulotomy under direct vision was performed in June, 1959. During the course of the operation cardiopulmonary bypass was employed for 25 minutes. All 3 commissures of a densely calcified valve were opened and a gratifying fall in the pressure gradient was apparent in the operative pressure records. Cultures of blood taken from the heart-lung machine after the operation grew *Candida guilliermondi*. Postoperatively the patient's course was apparently uncomplicated. He was given 1.0 Gm. of streptomycin daily for 5 days and 1.2 million units of penicillin daily for 13 days. He was discharged 16 days after operation. About 2 weeks later the patient experienced spiking fever which persisted in spite of antibiotics given by his physician. He was readmitted 6 weeks after operation. At this time numerous blood cultures showed *Staphylococcus aureus* and *Candida guilliermondi*. Antibiotic therapy was initiated promptly and the antifungal agent, amphotericin B, was also employed. Subsequent blood cultures became negative for *Staphylococcus aureus* but continued to show growth of the Candida. Since maximal doses of amphotericin were ineffective, another antifungal agent, designated RO-2, was employed separately and in conjunction with amphotericin and antibiotic agents. The progress of the infection was essentially unaltered, however, and the patient died 4 months after treatment was begun. Three vegetations, the largest of which was 2.5 cm. in diameter, were found on the aortic valve at autopsy (Fig. 1, *A* and *B*). *Candida guilliermondi* was cultured from the blood and the organisms were visible in microscopic sections (Fig. 1, *C* and *D*). Infected infarcts were found in the spleen and brain.

A more complete description of the clinical courses of these patients and the details of their therapy will be reported elsewhere.[1]

EXPERIMENTAL METHODS

In 14 mongrel dogs which weighed 11 to 24 kilograms, aortic regurgitation was created by the technique previously described by Roshe and Morrow.[8] After induction of anesthesia with thiopental sodium and endotracheal intubation, the right thorax was entered through the fourth intercostal space. During inflow occlusion, the ascending aorta was opened and a disc of tissue 3.9 mm. in diameter was excised from the base of the right coronary aortic leaflet. Circulation was restored and the aortotomy was closed. Four to 6 weeks after operation 12 of the animals were utilized for fungal inoculation and the 2 remaining ones served as uninoculated controls.

Initial studies in normal dogs were carried out to determine the magnitude of inoculum which would maintain a blood level of organisms for several minutes. After the intravenous injection of 32 million cells of *Candida guilliermondi* into normal dogs, it could be grown from blood sampled 5 to 10 minutes later. Consequently, all inoculations into the experimental animals consisted of 32 million or more organisms. Saline suspensions of cultures grown from the blood of patient H. D. were used as the source of *Candida guilliermondi*.

Three controls dogs which had not been operated on and 12 with aortic regurgitation were inoculated. The controls and 3 of those with aortic regurgitation were given no drugs. Of the remaining 9 dogs with aortic lesions, 5 were given 800,000 U. of penicillin and 0.5 Gm. of streptomycin intramuscularly on each of 8 days and 4 received 100 mg. of tetracycline intramuscularly daily for this period. In all animals venous blood cultures were drawn at weekly or biweekly intervals for a period of 3 months. At death, autopsy was performed immediately, and cultures of heart blood, of vegetations if present, and of apparently involved organs were obtained. Tissue was then placed in formalin and prepared for microscopic study.

RESULTS

The results of the study are summarized in Table I.

Inoculated controls with normal aortic valve. Negative blood cultures were obtained

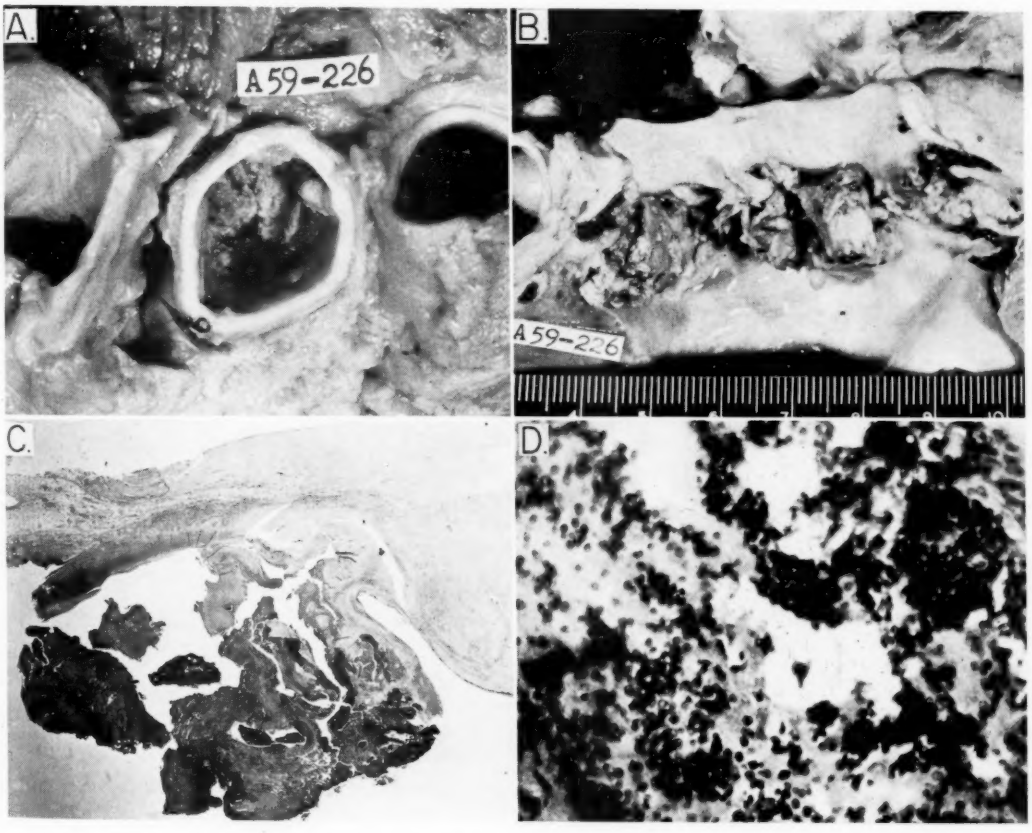

Fig. 1. Gross and microscopic photographs of the heart of patient H. D. *A*, The aortic valve as seen from above. Large fungating vegetations nearly occlude the valve orifice. *B*, The left ventricular outflow tract, aortic valve, and aorta have been opened. Vegetations nearly fill each aortic sinus of Valsalva. *C*, Microscopic section through one of the vegetations (PAS; ×10). The darker areas are colonies of Candida. The ventricular surface of the aortic cusp is free of vegetation. *D*, High power view of one of the colonies of Candida shown in C. (PAS; ×495). Only spore forms are present and hyphae are absent.

Table I. *Results of intravenous inoculation of Candida guilliermondi in dogs*

Group	No. of dogs	During life		At autopsy	
		Positive blood cultures	Signs of illness	Positive blood or tissue culture	Valvular vegetations
Inoculated controls, normal aortic valve	3	None	None	None	None
Inoculation, aortic regurgitation, no antibiotics	3	None	None	None	None
Inoculation, aortic regurgitation, penicillin and streptomycin	5	4	2	3	3
Inoculation, aortic regurgitation, tetracycline	4	1	1	1	1
Aortic regurgitation, no inoculation, no antibiotics	2	None	None	None	None

in all animals over the entire period of observation. The dogs gained weight, were active, and showed no signs of being ill. At postmortem examination none had evidence of endocarditis or other diseases attributable to the inoculation of the organisms.

Inoculation, aortic regurgitation, and no antibiotics. These 3 animals showed no positive blood cultures over 7 test periods. They gained weight and showed no evidence of being ill. At sacrifice no evidence of active endocarditis was present. The right coronary leaflets were scarred and thickened. The holes in them were rimmed by fibrous tissue. In one animal the perforation in the valve was healed. The viscera were free of signs of emboli.

Inoculation, aortic regurgitation, and administration of penicillin and streptomycin. Four of these 5 animals evidenced at least 1 positive blood culture during 6 sampling periods. Two showed repeatedly positive cultures. One dog died 6 days after inoculation, apparently in heart failure. At postmortem examination pleural fluid was present and the heart was dilated. A small (6 mm.) vegetation was present around the regurgitant orifice in the right coronary cusp. The spleen contained septic emboli. Cultures of heart blood and of the spleen were positive for *Candida guilliermondi.* A second animal died 1 month after inoculation in severe heart failure with passive congestion. An ulcerative vegetation 1 cm. in diameter was present on the aortic valve. Infarcts were grossly evident in the spleen. Cultures of the vegetation on the right coronary cusp yielded *Candida guilliermondi* and a gram-negative bacterium. A third animal at sacrifice demonstrated a 2.4 cm. vegetation on the right coronary cusp which extended through the ventricular septum into the right ventricle, probably through a tract inadvertently made by the punch during operation (Fig. 2, *A* and *B*). There were infarcts in the kidneys and spleen. Cultures of the vegetation were positive for *Candida guilliermondi* and moniliform organisms were seen on microscopic section of the valve (Fig. 2, *C* and *D*). In the remaining animals the hearts were normal except for the regurgitant lesions in the aortic leaflets.

Inoculation, aortic regurgitation, and tetracycline administration. One of 4 animals showed a positive culture during the observation period. This animal did not gain weight but otherwise did not appear ill. At sacrifice a vegetation 0.5 cm. in diameter was present on the right coronary cusp. Culture of the vegetation was positive for *Candida guilliermondi* although no organisms were seen on microscopic section of the valve. In the remaining animals the hearts were normal except for the regurgitant lesions in the aortic leaflets.

Aortic regurgitation, no inoculation, and no antibiotics given. The hearts of these 2 animals showed no evidence of endocarditis.

The regurgitant orifices were patent and minimally scarred.

DISCUSSION

The experimental study described demonstrates that fungal endocarditis can be produced in the dog when a site for its localization is provided by damage to an aortic leaflet. Although the number of experimental animals in the study was not large the results imply that antibiotic administration after inoculation with *Candida guilliermondi* facilitated the development of the lesion. This finding was not a surprising one, since it is commonly observed that long-term antibiotic therapy increases susceptibility to fungal infection in other areas of the body.[9] The selection of penicillin, streptomycin, and tetracycline in the investigation was based solely on the fact that postoperative patients commonly receive these drugs. The dosage employed was arbitrary. It is possible that other antibiotics or dosage schedules might alter or enhance the experimental occurrence of the lesion.

All 3 patients whose cases are reported had been treated prophylactically with penicillin and streptomycin and again one must speculate as to the role of these agents in the development of the infections. It has recently been advocated that antibiotics not be given routinely after cardiovascular oper-

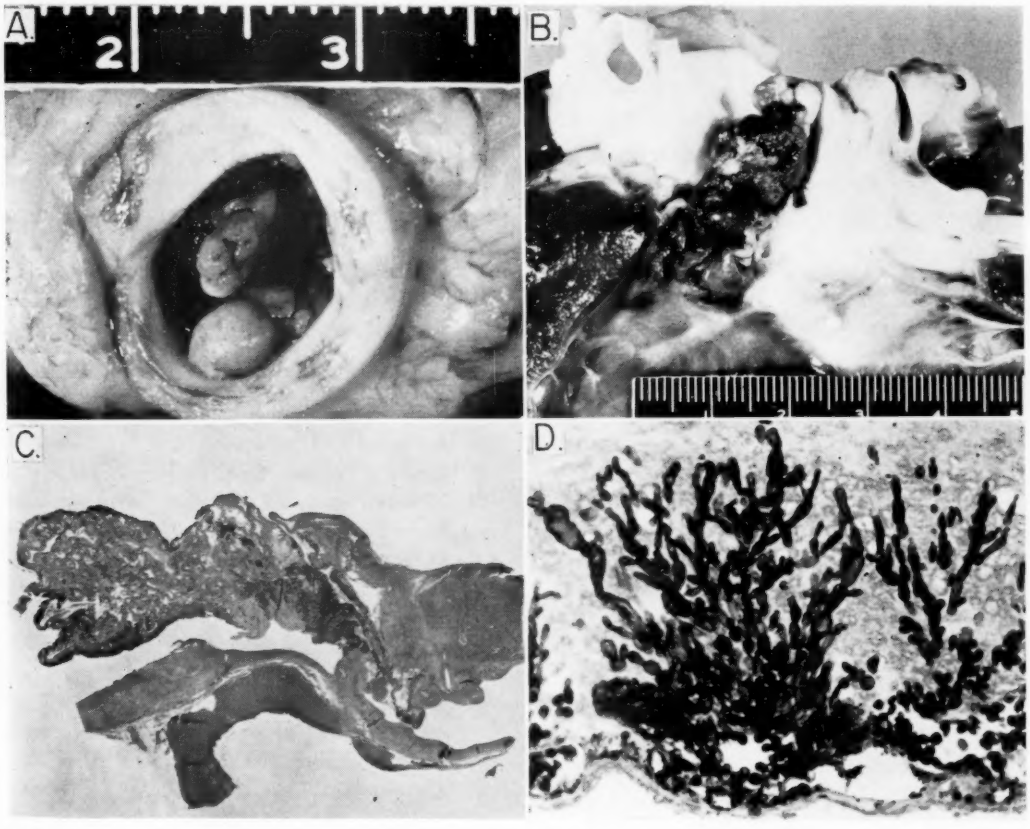

Fig. 2. Gross and microscopic photographs of the heart of a dog in which mycotic endocarditis was experimentally produced. *A,* The aortic valve as seen from above. A large vegetation obstructs the valve orifice. *B,* View taken after the left ventricle, aortic valve, and aorta were opened. The vegetation arises in the right coronary aortic cusp, which had previously ben perforated, and protrudes into the ascending aorta. *C,* Microscopic section through the vegetation demonstrated in *B.* (Hematoxylin and eosin; ×4). The darker areas are colonies of Candida. *D,* High power photomicrograph of Candida organisms (Methenamine silver; ×515). The hyphae forms are predominant here as contrasted to the spore forms shown in Fig. 1.

ations,[5] but until wider experience has validated this suggestion it is unlikely that the practice will be widely embraced. Prevention of endocarditis, therefore, depends upon minimizing the opportunity for inoculation, particularly at operation. In one of the 3 patients described, *Candida guilliermondi* was obtained from culture of the pump-oxygenator blood at the termination of operation and suggested a source of contamination in the operating room. An extensive bacteriologic survey, however, yielded no positive cultures for Candida from any furnishings, supplies, equipment, or instruments. Each patient had had cardiac catheterization shortly before operation and it was thought that the organism might have been introduced at this time and that the infections were already established at the time of operation. The organism was never found during a detailed survey in the catheterization laboratory, however, and the source of the organisms remains obscure.

Recognition of fungal endocarditis before death in these patients was possible because of awareness of its occurrence and of the practice of routinely inoculating blood cultures into media suitable for the growth of fungi as well as bacteria. Although success in treating Candida endocarditis has not been reported, early recognition of the disease will certainly permit a study of its natural history and provide opportunity for the trial of more effective agents as they become available.

SUMMARY

Three patients are described in whom endocarditis due to a "nonpathogenic" Candida occurred after operations for acquired heart disease. In each the disease was recognized in life but therapeutic measures were in vain. This experience suggested an experimental study in which fungal endocarditis was produced in dogs rendered vulnerable to infection by the previous production of aortic regurgitation. Endocarditis due to Candida only occurred in animals which were given antibiotics after inoculation with the organism, which suggests a relationship between the use of these agents and the occurrence of the disease. This method for the experimental production of fungal endocarditis may provide a useful preparation for studies of new chemotherapeutic agents developed for the treatment of this presently universally fatal infection.

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Surgical management of mycotic aneurysms

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An aneurysm which results from infection in the wall of an artery is currently regarded as a "mycotic aneurysm." Osler[18] is credited with originating the term. In 1885 he described a 30-year-old man with malignant endocarditis who, at autopsy, was found to have 4 separate aneurysms of the aortic arch which were caused by "mycotic endarteritis." Although syphilitic aneurysms arise from the action of micro-organisms on the arterial wall, they are commonly differentiated from the mycotic variety. Review of the literature shows rather loose usage of the term "mycotic" in reference to lesions of blood vessels. In general, all aneurysms which result from the presence of bacteria or fungi are accepted as belonging in the mycotic group. The object of this paper is to report our experience with 5 cases of this rare type of aneurysm and to stress the important features of surgical management.

CASE REPORTS

Case 1. E. B., a 31-year-old woman, was admitted to the hospital in June, 1948, with the chief complaint of low-back pain of 5 months' duration. There was no history of any previous illness. On physical examination a tender pulsatile mass was found in the region of the umbilicus. A systolic bruit was present. At operation a fusiform aneurysm of the abdominal aorta was found surrounded by dense inflammatory tissue. Biopsy of tissue surrounding the aneurysm showed acute inflammation. Proximal aortic constriction was instituted with the use of a rubber band wrapped in polyethylene film. A bilateral lumbar sympathectomy was performed. There was complete relief of back pain. When last seen in May, 1959, the patient was free of symptoms.

Case 2. S. K., a 25-year-old man, was admitted to the hospital with the diagnosis of subacute bacterial endocarditis. There was a history of rheumatic fever between the ages of 10 and 14 years. He appeared as a thin, pale, chronically ill patient. The temperature was 38.3° C. and pulse 100. Two fresh petechiae were seen in the left fundus. Blood cultures showed *Streptococcus viridans*. Two weeks after admission the patient developed a painful pulsatile mass in the lateral aspect of the right thigh. Operation showed a saccular mycotic aneurysm involving the descending branch of the lateral circumflex artery. The aneurysm was excised. At a follow-up visit 1½ years later, the patient was found to be well.

Case 3. L. E., a 12-year-old Chinese girl, was admitted to the hospital on Jan. 7, 1953, with the diagnosis of subacute bacterial endocarditis. She had acute rheumatic fever 4 years previously. Mitral insufficiency, mitral stenosis, and aortic stenosis were present. While being treated with bed rest and antibiotics, the patient experienced the gradual onset of periumbilical pain 2 weeks after admission. One week later a tender pulsatile mass was felt above the level of the umbilicus. At operation an aneurysm of the superior mesenteric artery was found. This was surrounded by dense inflammatory tissue. No further operative procedure was attempted because of aneurysmal involvement of all primary branches of the artery and the critical condition of the patient. Immediately after the operation, the patient was completely free of abdominal pain. The abdominal mass became firm, decreased in size, and was non-

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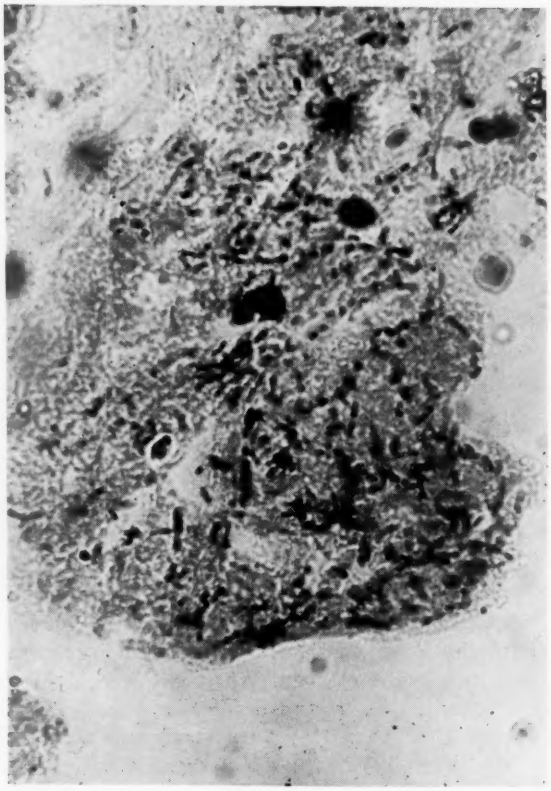

Fig. 1. Microscopic section of blood clot contained in mycotic aneurysm in Case 4. Gram-negative rod-shaped bacteria were identified as *Salmonella choleraesuis.*

pulsatile. Two years later the abdominal mass had completely disappeared and the patient was free of symptoms.

Case 4. E. Y., an 80-year-old man, was admitted to the hospital on Aug. 2, 1956, with a tender pulsating mass in the left thigh which had been present for 2 days. Physical examination showed a large (10 cm. diameter) pulsatile mass in the medial aspect of the midportion of the left thigh. The overlying skin appeared red and tense. Because of rapid expansion of the mass an emergency operation was required on the second hospital day. A large false aneurysm was found arising from the distal aspect of the superficial artery. This was excised and the resulting arterial defect was bridged with an arterial homograft. Disruption of the homograft occurred 5 days later. A culture of the aneurysm revealed *Salmonella choleraesuis* (Fig. 1). The homograft was removed and the artery was ligated. Two months later a second arterial perforation occurred at the site of previous ligature. *Salmonella choleraesuis* was again cultured from the artery. The wound healed. Four months later low thigh amputation was necessary for progressive ischemia of the left foot.

Case 5. C. M., a 30-year-old housewife, was admitted to the hospital on March 17, 1959, because of pain and swelling in the right popliteal area of 2½ months' duration. A heart murmur had been discovered 2 years prior to admission. There was no history of rheumatic fever. Physical examination showed a Grade II systolic murmur in aortic and mitral areas. Temperature was 38° C. There was a tender pulsatile mass (6 by 5 cm.) in the right popliteal space (Fig. 2). During 2 weeks of observation, the aneurysm gradually enlarged. Thorough study failed to show the etiology of the aneurysm. Nine negative blood cultures were obtained and the fever continued unchanged. A right lumbar sympathectomy was performed. Four days later the popliteal aneurysm was excised (Fig. 3). The resulting arterial defect was bridged by a plastic arterial prosthesis (woven Teflon). Culture of the aneurysm showed streptococcus. The patient was given large doses of penicillin and streptomycin and the fever gradually returned to normal. When seen 2 years later she was asymptomatic. The graft continues to function well.

DISCUSSION

A patient with a mycotic aneurysm usually presents a dual problem in therapy; namely, the antibiotic treatment of bacterial endocarditis or septicemia, and the surgical treatment of aneurysm. Prior to the availability of antibiotic drugs, surgical procedures for mycotic aneurysms associated with bacterial endocarditis tended to complicate the course or precipitate the termination of an almost invariably fatal disease. Today the antibiotic drugs have led to a situation in which the surgeon is called to treat an aneurysm in the presence of manageable endocarditis or septicemia.

Spontaneous cure of mycotic aneurysms has rarely occurred.[16, 18] Case 3 is a striking example of the spontaneous disappearance of an aneurysm which may occasionally occur. In this instance, a 12-year-old girl with subacute bacterial endocarditis developed an aneurysm of the superior mesenteric artery. Surgical exploration and biopsy confirmed the presence and nature of the aneurysm. Because of the unfavorable location of the aneurysm, the marked local inflammatory reaction, and the critical condition of the patient, a further surgical procedure was not attempted. Postoperatively, the

patient was remarkably free of the pain and the aneurysm was felt to be smaller and firmer. Presumably thrombosis occurred. When last seen 2 years later this patient had no evidence of aneurysm.

In addition to being usually associated with a blood stream infection, mycotic aneurysms differ from the syphilitic and arteriosclerotic varieties in several important respects. Occurring commonly in young people, the infected aneurysm is usually found in an otherwise normal arterial tree which has an excellent capacity for the development of collateral circulation and responds well to sympathetic denervation. Second, the rapidly developing type of mycotic aneurysm which may proceed to rupture within a few days, as in Case 4, demands an urgency of surgical treatment not usually necessary in other types of aneurysms. Third, special surgical considerations regarding the technical handling of the aneurysm and adjacent arteries are prompted by the fact that the operation is necessarily performed in an infected field.

A variety of surgical procedures have been used in the treatment of mycotic aneurysms (Table I). Proximal (Hunterian) ligation or proximal and distal ligation with or without excision proved to be the most acceptable methods before the antibiotic era. In view of the septic nature of the condition and the failure of antibiotic therapy to consistently eliminate infection from the aneurysm, we believe that excision of the sac is a primary objective. When the aneurysm is located in a noncritical artery, that is, one in which ligation does not appreciably alter function or viability of the part it supplies, it is usually well treated by simple ligation and excision. This is illustrated by Case 2. Even when located in more critical sites, such as the superior mesenteric, common iliac, and femoral arteries, good results have been obtained after extirpation of the aneurysm with proximal and distal ligation of the artery.[1, 4, 9, 19] Success in these instances was attributed to development of collateral arterial channels secondary to gradual vascular occlusion associated with the aneurysm.

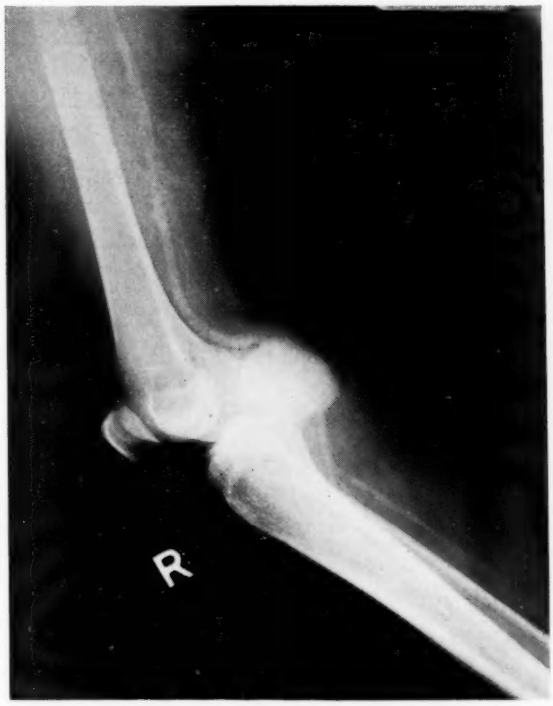

Fig. 2. Arteriogram shows the aneurysm of the popliteal artery described in Case 5.

Fig. 3. Exposure of the mycotic popliteal aneurysm in Case 5 at operation.

Table I. *Cases of mycotic aneurysm treated surgically*

Year reported	*Author*	*Age*	*Sex*	*Artery involved*	*Procedure*	*Result*
1908	Clutton and Dudgeon	78	M	Femoral	Proximal ligation; incision and drainage	Good, 3 mo. follow-up
1908	Stern	20		Superior mesenteric	Ligation above and below; evacuation and packing	Died 6 wk. later from second aneurysm
1909	Lewis and Schrager	43	M	Brachial	Proximal ligation	Died 7 mo. later
1929	Osius	28*	M	Popliteal	Excision	Amputation 3 days later
1934	Gage	18	F	Common iliac	Proximal ligation	Alive 3 mo. later, limb survived
1939	Rogers		M	Radial	Excision	Died later, cardiac failure
1943	Martorell and Serra	32	M	Common femoral	(1) Ligation external iliac; (2) ligation and excision	Died of subacute bacterial endocarditis in 3 mo.
1946	Klein and Crowell	22	M	Ulnar	Excision	Cure
1947	Blakemore	39	F	Common femoral	Vitallium tube vein graft	Good over 1 year
1948	Hurwitz and Arst	20	M	Brachial	Excision	Cure
1948	Julian	27	M	Femoral	Sympathectomy, excision	Good, 8 mo. follow-up
1949	Goadby et al.	35	M	Femoral	Ligation, excision	Good, died of subacute bacterial endocarditis 7 mo. later
1950	Demirleau	27	F	Common femoral	Endoaneurysmorrhaphy	Good, 8 mo. follow-up
1951	Gerner and Fischer	30	F	Femoral	Ligation, excision	Good, developed intra-abdominal aneurysm 2 yr. later
1951	Rogers	23	M	Femoral	Sympathectomy, aneurysmorrhaphy	Good
1952	Fernbach et al.	10	F	Common iliac	Proximal and distal ligation	Good, 2 mo. follow-up
1953	Harrison and Desmond	45	F	Popliteal	Proximal ligation	Well more than 1 yr. later
1953	Tresidder and Warren	25	F	Posterior tibial (bilateral)	Excision (bilateral)	Good
1953	De Bakey and Cooley	27	F	Superior mesenteric	Resection	Well, 3½ yr. later
1954	Shnider and Cotsona	45	M	Ulnar	Ligation, excision	Good
1954	Barker	24	M	Deep femoral (bilateral)	Ligation, excision	Good, 3 mo. follow-up
1954	West	23*	F	Common iliac	Ligation, partial excision	Good, follow-up 43 days
1954	West	23*	F	Superior mesenteric	Restorative aneurysmorrhaphy	Good, follow-up 26 days
1955	Moore and Telling	21	F	Common iliac	Bifurcation homograft; aneurysm not resected	Good, 3 yr. follow-up
1955	Shea et al.	58	M	Common carotid	Excision with end-to-end anastomosis	Good, 1½ yr. follow-up
1955	Rogers	29	M	Femoral (bilateral)	Hunterian ligation of external iliacs	Good
1956	Hankins and Yeager	76	M	Superficial femoral	Ligation and excision	Good, follow-up several months

*Probably mycotic, but lacking positive identification.

Table I. *Cont'd*

Year reported	*Author*	*Age*	*Sex*	*Artery involved*	*Procedure*	*Result*
1957	Katz and Jacobson	21	F	Superior mesenteric	Ligation, excision, small bowel resection	Good, 8 mo. later
1957	Sullivan and Mangiardi	26	M	Brachial	Excision with end-to-end anastomosis	Good, follow-up 6 mo.
1957	Smith and Hutchinson	78	M	Superficial femoral	Excision of sac, repair of artery	Good, death from myocardial infarction 6 mo. later
1957	Smith and Hutchinson	46*	M	Common carotid	Excision of sac, repair of artery	Good, 3 yr. follow-up
1958	Zak	58	M	Femoral	Excision with arterial homograft	Recurrent hemorrhages from operative site, died of coronary thrombosis 1 yr. later
1958	Zak	55	M	Femoral	Excision with arterial homograft	Unknown
1958	Zak	61	M	Abdominal aorta	Excision of ruptured aneurysm, arterial homograft	Death, 2 weeks
1958	Lovezzola	34	M	Mesenteric artery	Excision	Good, 2 yr. follow-up
1959	Horton	31	M	Ileocaecal branch superior mesenteric artery	Excision with right hemicolectomy	Good
1960	Authors	31*	F	Abdominal aorta	Proximal sclerosing band	Good, 11 yr. follow-up
1960	Authors	25	M	Lateral circumflex femoral	Excision	Good, 1½ yr.
1960	Authors	80	M	Superficial femoral	(1) Excision with arterial homograft; (2) removal of graft, proximal and distal ligation	Initially good, amputation 5 mo. later
1960	Authors	30	F	Popliteal	Excision, plastic graft (Teflon)	Good, over 2 yr.

In an effort to achieve optimum function as well as viability, various arterial reconstructive methods have been used in the treatment of mycotic aneurysms (Table II). Endoaneurysmorrhaphy, although successfully used in 3 reported instances, carries the undesirable feature of leaving an infected aneurysmal sac in situ.[6, 19, 26] Furthermore, an inflamed and frequently necrotic aneurysm may make the procedure technically impossible. Excision of the sac with lateral repair of the artery was used successfully in 2 cases by Smith and Hutchinson[22] in treating mycotic aneurysm of the femoral and carotid arteries. This method is most applicable if the communication between artery and aneurysm is small and the remaining arterial wall appears to be normal. In instances in which an appreciable part of the circumference or length of the arterial channel is involved in the infective process, excision of the artery is necessary and restoration of arterial flow is only possible by end-to-end anastomosis or the interposition of an arterial graft. In Case 5 an arterial homograft was used to re-establish arterial flow after excision of a mycotic aneurysm (Salmonella) of the superficial femoral artery. In this instance disruption of the proximal anastomosis resulted from infection of the graft and required removal of the graft. Zak[28] has called attention to the syndrome of rupture of previously diseased large arteries in the course of enterobacterial

Table II. *Reconstructive surgical procedures used in the treatment of mycotic aneurysms*

Procedure	*No. of operations*	*Results*
Without graft		
Restorative aneurysmorrhaphy	3	Good
Excision with end-to-end anastomosis	2	Good
Excision with lateral repair of artery	2	Good
With graft		
Excision with Vitallium tube vein graft	1	Good*
Excision with arterial homograft	5	1 good, 2 disrupted, 2 unknown
Excision with plastic prosthesis (Teflon)	1	Good

*Graft occluded after 1 year.

(Salmonella) infections. He reported 3 instances in which the site of arterial infection was treated by excision and insertion of an arterial homograft. One of the cases in a femoral artery was followed by 8 episodes of massive hemorrhage from the operative site that necessitated regrafting operations. The fate of the other grafts was not stated. The undesirability of introducing a segment of nonviable organic material into an infected field is apparent.

That the plastic arterial prostheses are more acceptable grafts in the presence of infection is attested to by the experiments of Foster and associates.[4] After the deliberate infection of the retroperitoneal area of dogs with a suspension of canine feces, these investigators replaced segments of the abdominal aorta with arterial homografts and synthetic prostheses (nylon). All animals were given antibiotic drugs. Sixty-four per cent of the animals with plastic prostheses survived with functioning aortic substitutes as opposed to 17 per cent in the homograft series. However, there was evidence of residual and persistent infection around the synthetic tube in 5 of 25 long-term survivors. Harrison,[7] in an experimental study, found Teflon grafts to be preferable to homografts in the presence of infection or contamination. Case 5 illustrates the successful use of plastic prostheses (Teflon) after excision of a mycotic popliteal aneurysm (streptococcus).

Existing experimental and clinical studies have evaluated homograft and synthetic replacements in the presence of infection. Although on the basis of such studies the synthetic grafts appear to be superior, it is to be wondered if an autogenous vein graft might not be a very satisfactory replacement by virtue of the absence of foreign-body or antigenic reaction.

SUMMARY

1. Personal experiences with the surgical management of 5 cases of mycotic aneurysm have been presented.

2. All reports of surgically treated mycotic aneurysms have been reviewed.

3. The conclusions made were (a) excision with proximal and distal arterial ligation is the treatment of choice for a mycotic aneurysm located in a noncritical artery, (b) excision with either end-to-end anastomosis or lateral arterial repair is a very satisfactory means of treating a mycotic aneurysm located in a critical artery, and (c) On the basis of existing evidence a plastic prosthesis appears to be a more acceptable graft than a homograft for use in a contaminated or infected field (a successful case of Teflon graft replacement is reported). The comparative suitability of autogenous vein grafts under such conditions cannot be positively stated at this time.

We wish to acknowledge the permission of Dr. Arthur H. Blakemore, New York, New York, for the inclusion of Case 1 in this series.

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The second-look procedure in the management of ovarian malignancies and pseudomyxoma peritonei

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Cancer of the ovary occurs with relative frequency. In most series the peak incidence obtains in patients in their fifth and sixth decades. A completely satisfactory histopathologic classification of ovarian tumors remains an unsolved problem. The systems offered by Novak and Kottmeier[2, 3] probably have the widest acceptance. More distressing, of course, is the need for improved diagnostic and therapeutic measures. The magnitude of this need is made evident in the survival experience data presented at the Fourth National Cancer Conference.[1]

It is not our purpose to debate the indications for or optimal utilization of combined surgical and radiation therapy for cure of ovarian malignancy and related disease. A strengthened armamentarium permits more physiologic management after extensive surgical procedures. The need for extended and repetitive excisions follows from the great frequency with which local extension, lymph node metastasis, and even peritoneal implantation are found at the initial exploration. Moreover, cystadenocarcinoma and pseudomucinous cystadenocarcinoma of the ovary are relatively slowly growing tumors, a circumstance which fully justifies a vigorous surgical approach to their control and cure. A similar rationale of management is applicable to pseudomyxoma peritonei in association with carcinoma of the appendix or ovary.

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Since the institution in this clinic of systematic use of secondary operations after the original excision of a visceral cancer,[4] 14 patients (Table I) have been managed in the framework of the "second-look" program. The results have been such that an interim report is warranted.

PLAN OF MANAGEMENT

The concept of re-exploration for patients with visceral malignancy during an asymptomatic phase evolved from an experience with treatment of a carcinoma of the colon in a female patient. She underwent a series of operative procedures during the period from 1942 to 1951. These were carried out, however, only when recurrent disease was causing symptoms. The course of this patient made reasonable the planned program of re-operation during the asymptomatic interval, before the reassertion of symptoms, embodied in the second-look program begun in this clinic in 1949.

Details of the principles of this program have been given in a number of previous communications. Suffice it to say here that re-operation is carried out in patients known to be asymptomatic and without clinical evidence of cancer approximately 6 months after original excision of malignancies with gross or microscopic evidence of spread beyond the primary site. If possible, residual or recurrent tumor is removed in its entirety. Additional "looks" are employed, if necessary, to render the patient free of cancer.

In the event that painstaking exploration and biopsies at any of the secondary operations fail to show evidence of the disease, the systematic re-exploration at 6-month intervals is discontinued and further surgical effort is made only in the event of recurrence or in selected cases in which the original lesion was widespread.

RESULTS

Twelve of the 14 patients in this group had adenocarcinoma of the ovary and 1 a malignant ovarian teratoma. An additional patient had pseudomucinous involvement of the ovaries. The appendix was the probable primary site. The latter patient and 2 of the 12 patients with adenocarcinomas of the ovary had associated pseudomyxoma peritonei (Table I).

Two patients had no cancer at their first reoperation and are living and well. Two patients (C. H. and P. T.) with 2 or more positive looks are living and well without evidence of cancer. Two patients (E. Y. and M. D.) are living and well and are awaiting further operations since they had residual disease at their last look. An additional patient (B. O.) is living with carcinosis 5 years after a procedure thought to have effected conversion to the cancer-free state. Despite widespread metastases, she continued to lead an active and useful life until 1 month prior to this writing. Five patients died at intervals of from 19 to 50 months after their primary operations. There have been 2 postoperative deaths in this series.

CASE REPORTS

The following cases are illustrative of a program of systematic reoperation and the gratifying results that such an approach may achieve.

Case 1. C. H., a 41-year-old woman, was first operated upon in this hospital on Oct. 27, 1948. At that time, she had a huge cancer which involved both ovaries and the entire pelvic peritoneum, and had metastases to the mesentery of the small bowel. The patient underwent a complete excision of pelvic viscera except for the bladder, omentectomy, and a partial jejunectomy along with removal of the involved mesentery. She was then given to postoperative irradiation. She remained well for 10 years. However, in the early part of 1958, she returned with a history of hematuria and lower abdominal pain. On March 10, 1958, she again underwent exploratory operation and was found to have tumor in the right side of the pelvis which infiltrated the right ureter, the bladder and the wall of the rectum. There were metastases to the right external iliac nodes. There was no evidence of hepatic metastases. Excision of the tumor mass, partial cystectomy, right ureterectomy with right cutaneous ureterostomy and subtotal colectomy with inversion of rectal pouch, and descending colostomy were performed.

Subsequent to this operation, the woman developed an ileal fistula and a rectovaginal fistula as well as a transverse colon fistula. The latter fistulas were treated with an additional colostomy proximal to the 2 lesions and the ileal fistula was left alone.

On Oct. 29, 1958, another exploratory operation was performed. It was our purpose to carry out another look as well as close the multiple fistulas. Results of multiple biopsies were negative for cancer. The patient underwent closure of the colocutaneous fistula as well as the rectovaginal and vesicovaginal fistulas and resection of the terminal ileum with an ileoascending colostomy. A loop ileostomy proximal to the anastomosis was performed as well as a ureterostomy, cystostomy, and drainage of the rectal pouch. She developed recurrent fistulas but remained relatively well.

She was readmitted to the hospital on Feb. 22, 1960, for another attempt to close the fistulas. Because of an active duodenal ulcer, further surgical intervention was deferred. She has continued to do well despite the fistulas and is to come in shortly for closure of the various fistulous tracts.

Case 2. P. T., a 36-year-old white woman, was found on Nov. 20, 1957, to have a malignancy involving the right ovary and appendix with evidence of pelvic peritoneal implantation. Total hysterectomy, right salpingo-oophorectomy, appendectomy, and excision of the tumor implants were carried out. Histologically, the lesions were determined to be pseudomucinous adenocarcinoma of the ovary with pseudomyxoma peritonei. The woman was seen at the University of Minnesota Hospitals for the first time in December, 1958, and was found to be asymptomatic and without clinical evidence of recurrent or residual carcinoma.

Nevertheless, a second-look operation was performed on Dec. 11, 1958. There were multiple areas of recurrence in the pelvis with tumor adherent to the terminal portions of both ureters. In addition, a 6 by 7 by 3 cm. mass and several smaller nodules were present in the right subphrenic space. All visible tumor was excised. The patient did well in the postoperative period.

Table I. *Second-look results in cases of ovarian neoplasm*

Status	*Patient*	*Diagnosis*	*Age at and date of first operation*	*Course*
Living and well, negative second look	F. B.	Papillary cystadenocarcinoma	47, Aug. 6, 1952	Negative look Feb. 13, 1953; also negative at cholecystectomy Nov. 18, 1953
	G. O.	Cystadenocarcinoma	48, Jan. 7, 1959	Negative look July 8, 1959
Living and well, converted	C. H.	Cystadenocarcinoma	41, Oct. 27, 1948	Positive look March 10, 1958; positive look; negative look; Oct. 29, 1958
	P. T.	Pseudomucinous cystadenocarcinoma (pseudomyxoma peritonei)	36, Nov. 20, 1957	Positive look, positive look, negative look
Living and well, awaiting another look	E. Y.	Adenocarcinoma (mesonephroma type)	54, April 15, 1957	Positive look Nov. 26, 1958
	M. D.	Papillary cystadenocarcinoma	57, Sept. 10, 1958	Negative look May 10, 1959; positive look Feb. 1, 1961
Living with residual disease	B. O.	Pseudomyxoma peritonei, ovary or appendix probable primary site	40, July 6, 1944	4 positive looks; negative look in 1955; carcinomatosis Oct., 1960
Dead of cancer	E. W.	Malignant teratoma	34, Jan. 2, 1949	7 positive looks; died in March, 1952
	S. K.	Cystadenocarcinoma	47, Sept. 12, 1949	2 positive looks; died in July, 1951
	M. Z.	Cystadenocarcinoma	57, June 7, 1950	Positive look Oct. 27, 1951; negative look Jan. 21, 1952; carcinosis Oct. 16, 1952; died in April, 1953
	L. S.	Papillary cystadenocarcinoma	49, May 20, 1954	4 positive looks; died in March, 1956
	S. L.	Serous cystadenocarcinoma	50, March 5, 1946	3 positive looks; died in October, 1951
Postoperative deaths	K. D.	Pseudomucinous cystadenocarcinoma (pseudomyxoma peritonei)	76, Nov. 24, 1954	Carcinomatosis at look Aug. 1, 1955; died during convalescence
	T. B.	Papillary cystadenocarcinoma	51, July 16, 1958	Carcinomatosis at look Jan. 22, 1959; died during convalescence

Upon admission to the hospital in October, 1959, she was again without symptoms or evidence of residual or recurrent carcinoma. At operation in October, 1959, carcinoma was found in the subhepatic space, omentum, left perirenal fat, and near the hilum of the spleen. Splenectomy and omenectomy and excision of all visible tumor were carried out. There was microscopic evidence of carcinoma in 17 of 32 submitted specimens.

On September 26, 1960, she again underwent exploratory operation. Multiple biopsy specimens were taken throughout the peritoneal cavity. The final pathologic report indicated no evidence of residual carcinoma. The patient remains well.

Case 3. E. Y. was a 57-year-old woman. At another hospital on April 15, 1957, she underwent a total hysterectomy and bilateral salpingo-oophorectomy, with removal of a very large fluid-filled cyst. The pathologic diagnosis was adenocarcinoma of the ovary, mesonephroma type. On Nov. 26, 1958, the patient came to this hospital. She was completely asymptomatic. Exploratory operation showed only cholelithiasis. There was no gross evidence of recurrence. However, a peri-

aortic lymph node dissection was performed in addition to cholecystectomy and appendectomy. Two of 6 periaortic nodes contained carcinoma. In addition, a small nodule in the remainder of the left broad ligament was also positive for recurrent disease. The patient has remained entirely well.

Our experience with this disease has been such that on several occasions we have suggested that her consent to undergo another exploratory operation would be in her best interest. She has to date been unable to accept this recommendation, but recently suggested she will consent to the operation.

Case 4. In July, 1944, B. O., a 40-year-old woman, had a gelatinous periumbilical mass removed at another hospital. The specimen was said to show "low-grade adenocarcinoma." In February, 1952, she underwent a second exploratory operation and copious amounts of mucogelatinous material were removed. The pathologic diagnosis was pseudomyxoma peritonei. The patient first came to the University of Minnesota Hospitals in February, 1954. She complained of abdominal distention, constipation, and diarrhea. On Feb. 26, 1954, she was operated upon and was found to have 3 L. of gelatinous material in the abdomen. The appendix was removed and was found to show adenocarcinoma. There were also extensive pelvic peritoneal metastases. It was believed that this was a palliative procedure and the patient therefore received postoperative radiation therapy.

On June 9, 1954, during an asymptomatic period, she again underwent exploratory operation. She had a massive tumor in the pelvis attached to the anterior surface of the rectum, filling the cul-de-sac, and adherent to the uterus and urinary bladder. The parietal peritoneum, lateral and anterior abdominal walls, the capsule of the right lobe of the liver, and the serosal surface of the small bowel were found to contain metastatic tumor. A total hysterectomy, left salpingo-oophorectomy, resection of pelvic peritoneum and all palpable tumor, and a left transverse colostomy were performed at that time. She then remained well until December, 1954. At that time she returned during an asymptomatic phase and underwent another exploratory procedure. No malignant cells were found on exploration, but semiadherent mucinous material was distributed over portions of the jejunum, the cecum, the pelvic colon, the pelvic portion of the left ureter, and in the area of the gall bladder. Multiple biopsy specimens were taken and 5 of 15 were positive for mucin. Therefore, on Oct. 13, 1955, again during an asymptomatic phase, the patient underwent exploratory operation. The remaining appendical stump was removed and 19 biopsy specimens taken. Pathologic examination showed residual mucinous adenocarcinoma in the appendical stump. The other specimens, including liver biopsy material, were negative for carcinoma. The woman was followed closely in the clinic.

In August, 1960, she returned because of the appearance of an enlarging mass just above the symphysis pubis due to a recurrence in the anterior abdominal wall. Roentgen examination of the chest showed widespread pulmonary metastases. The mass was excised and proved to be recurrent adenocarcinoma. The patient had, in addition, such extensive intraperitoneal carcinosis that any further attempt at excision was precluded. She received radiation therapy after convalescence. At this time she has reached the terminal stages of the disease.

Case 5. M. D., a 57-year-old woman, was first operated upon at the University of Minnesota Hospitals on Sept. 6, 1958. Total hysterectomy and bilateral salpingo-oophorectomy were performed with removal of a papillary cystadenocarcinoma which involved both ovaries. There were extensive metastases along the entire length of the ovarian vessels up to the site of their origins. These were removed and periaortic and peri–vena cava lymph node dissections were carried out. A second-look procedure was carried out on May 10, 1959. Biopsy specimens from the pelvis, small bowel mesentery, porta hepatis, and retroduodenal area were negative for recurrence.

The patient continued to do well. Because of the disappointing experience with B. O., and because of the extent of the disease in this patient at the first operation, she was urged to undergo another exploration. On Feb. 1, 1961, 22 months after a "negative look" and while she was completely asymptomatic, the woman underwent another exploratory operation. There was recurrent tumor overlying the right internal iliac vein and in the perirenal fat pad near the inferior pole of the left kidney. These were excised and a splenectomy and wide dissection of both lateral parietes were carried out. Another look will be undertaken after 2 years, to which suggestion the patient already has assented.

DISCUSSION

Recent data show that if all stages of the disease are considered, 20 to 25 per cent of patients treated for carcinoma of the ovary will survive for 5 years or more. Of those with cancer confined to the ovary at the time of diagnosis and institution of treatment, 60 to 65 per cent will be alive for 5 years.

Unfortunately, approximately 50 per cent

of ovarian cancers are found to have spread beyond the primary site at the time of original exploratory operation. The failure of radical primary operation to achieve cure in these cases continues to plague those concerned. Moreover, the combination of surgical and radiation therapy and adjunctive chemotherapy has not effected significant improvement in cure rate.

The accomplishment in many of the patients with extensive cancer has been gratifying. It is fair to say that a program of systematic secondary operation has served to alter the prognosis of patients "converted" by repeated surgical intervention. Prolongation of life has been achieved in a number of patients in whom resection of metastatic cancer prevented imminent death due to gastrointestinal or urinary tract obstruction.

The information obtained through application of these principles of management is of value to physicians and patients alike. The findings at the time of first re-operation has lent support to a widely recognized need for change in the initial operative procedure for some cancers. In addition, the experiences with 2 patients who have been declared cancer-free only to develop recurrences—one in whom the disease was "caught" in time, the other with disease out of hand at the time of exploration, indicate that some of these lesions are relatively slow-growing tumors. When a patient has been rid of very extensive disease through the second-look procedure, an additional delayed look, perhaps 2 years after one negative look, is in order to consolidate the gain.

SUMMARY

The experience with the second-look procedure in the management of ovarian malignancies and pseudomyxoma peritonei is reviewed. Four of 13 patients with ovarian carcinomas, including one with associated pseudomyxoma peritonei, are alive and well after intervals of from 2 to 12 years after the initial operative procedure. Two of these 4 are considered to have been converted to the cancer-free state after 3 looks, while 2 who are probably converted are awaiting another look.

The second-look procedure appears to have merit in the management of ovarian malignancies and pseudomyxoma peritonei.

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Pathologic lesions in experimental hypernatremia induced by extracorporeal dialysis

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Hypernatremia will be encountered in any clinical situation in which the balance of water and sodium in a patient results in a persistent gain of sodium in relation to water. This may result either from losses of water in excess of losses of sodium, or from excess of sodium intake in relation to water intake, or from a combination of these events.

While hypernatremia is not observed so commonly by the surgeon as is hyponatremia, it is not a rare electrolyte disturbance, and has been found in infants with diarrhea,[7, 14, 15] in patients with heat stroke,[2] in association with intracranial lesions,[6, 16, 17] after neurosurgery,[16, 18] in the diuretic phase after renal failure,[12] in uncontrolled diabetes insipidus,[6] and during treatment of diabetes mellitus.[4] It has also been described in association with gastrointestinal bleeding,[3] and with overenthusiastic feedings of high caloric–high solute diets by nasogastric tube.[5] The mechanism which contributes to the increasing concentration of sodium in these various clinical situations differs somewhat, but the ultimate serum electrolyte pattern achieved is the same.

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Hypernatremia is more often found in the very young and in the very old, or in patients with impaired renal function.[20] In all of these instances renal concentrating power is decreased, a more dilute urine excreted, and the tendency to accumulate sodium in excess of water is enhanced.

The clinical syndrome which accompanies hypernatremia is marked by malaise, restlessness, confusion, hallucinations, and convulsions.[7, 13, 20] These symptoms have drawn attention to the central nervous system, and an increasing body of clinical and experimental data indicate that definite subdural and intracranial lesions may accompany the hypernatremic state.[13, 14, 20]

Some clinical reports have suggested that renal damage also occurs,[2, 12] but the causal mechanism of the renal lesions observed is confused by the fact that most of the patients with these changes have been in shock for some time before death, or were the victims of overdoses of sulfonamide drugs.

Experimental studies of hypernatremia in the past have involved significant changes in the fluid volume of the subject, either by overhydration or by dehydration (and usually both, sequentially). Such volume changes have been necessarily accompanied by circulatory changes which are also seen

in physiologic disturbances which do not involve hypernatremia. This has made analysis of the resultant pathologic process difficult in that some of the changes could well have been circulatory in origin. The present study had as one of its goals the inducement of hypernatremia without changing body water volume and without permitting changes in concentration of extracellular ions other than sodium and chloride. This report describes the use of extracorporeal dialysis as an experimental tool, and presents some of the results obtained.

MATERIALS AND METHOD

Mongrel female dogs which weighed 18 to 20 kilograms were used. The dogs were anesthetized with a combination of sodium pentobarbital, 10 mg. per kilogram, and gallamine triethiodide (Flaxedil), 2 mg. per kilogram, given intravenously. After the initial use of pentobarbital, the animals were maintained entirely with gallamine triethiodide throughout the several hours of the experiment. The total dose amounted to approximately 2 mg. per kilogram per hour. After induction of the anesthesia an endotracheal tube was inserted and respirations were maintained by a piston respirator at a rate of 400 c.c. of room air per kilogram per minute.

The dogs were placed on an infant scale with a large pan. The femoral artery and vein of both legs were exposed. The artery and vein on one side were connected to the appropriate arterial and venous sides of a Kolff disposable coil artificial kidney. The artery of the other leg was connected to a mercury manometer, and the vein was connected to an infusion bottle. The animal was given no heparin directly, but approximately 50 mg. of heparin per 500 ml. was added to the priming blood in the disposable coil.

Electrolytes were added to the 100 L. of fluid in the artificial kidney bath to give a concentration approximating the extracellular fluid concentration of electrolytes in the dog—sodium 150, chloride 126, carbon dioxide 27, magnesium 2.1, calcium 7.2, and potassium 4 mEq. per liter. The pH was maintained at 7.4 by bubbling 5 per cent carbon dioxide through the bath. The total osmolality of the solution was 315 milliosmols per kilogram of water. This solution will be referred to as the normal bath. Creatinine was added to the bath to give a concentration of 5.8 mg. per cent. The infusion which the dog received in the contralateral vein contained a similar concentration of sodium, chloride, and carbon dioxide. A No. 14 Fr. Foley catheter, with a 5 c.c. bag, was placed in the dog's bladder. The bag was inflated and the catheter led to a graduated cylinder. The arrangement of the experiment is illustrated in Fig. 1.

After this preparation, the animals designated as controls were dialized against the normal bath for periods of from 5 to 7 hours. Since the Kolff disposable coil has 2 parallel units of dialysis tubing, 2 dogs were usually dialyzed against the same bath during each experiment. Blood flow was maintained between 200 and 300 ml. per minute. Blood and urine samples were taken before the dialysis started, and usually each hour during the experiment. Plasma was promptly separated from cells and stored under oil. These samples were analyzed for osmolality by a Fiske osmometer, for chloride by a Cotlove chloridimeter, for sodium and potassium by an internal standard flame photometer, for creatinine by the method of Hare and Hare,[11] for total proteins by the method of Greenberg,[10] and for plasma urea nitrogen by the method of Archibald.[1] Plasma water was determined by weighing an aliquot and drying to constant weight. Electrolyte concentrations are expressed in milliequivalents per liter of plasma water, corrected by a Donnan factor of 0.96. Hematocrits were also obtained at intervals by the method of Wintrobe.[19]

In some of our early experiments it was found that there was difficulty with a sudden drop of the dog's blood pressure during the initial period of the dialysis. This was reflected in a drop in the dog's glomerular filtration rate and urinary output. Two modifications in our techniques succeeded in eliminating this difficulty. One was the use

of gallamine triethiodide to maintain the animal throughout the experiment, after pentobarbital anesthesia during the initial manipulations. The second was scrupulous care in preventing or compensating for fluid losses from the body while the dog was being dialyzed. Although the Kolff coil is semirigid, its volume does tend to increase somewhat as the blood flow through the coil is increased. This will be reflected in the first 10 or 15 minutes of dialysis by a drop in the blood pressure of the dog and a decrease in the dog's weight. By our technique, this shift of blood from dog to coil could be completely avoided. Prior to dialysis, the coil was primed with the arterial and venous cannulae connected together and the flow rate through the coil was adjusted during this priming period to the level planned for use during the experiment. With this method, the coil takes up a maximum amount of priming blood, usually 750 ml. to each half of the coil, or a total of 1,500 ml. When dialysis was started, the flow rate was slowly increased to the expected maximum over the first 10 or 15 minutes, and the dog's weight was carefully watched. Any weight loss over this period was promptly corrected by infusion of additional blood into the coil. An additional 100 to 200 ml. of blood may be required.

A second source for fluid loss is the ultrafiltration through the semirigid Kolff coil. This amounts to approximately 220 ml. per hour, per dog, at the flow rates used. A portion of this loss is probably also due to osmotic shifts between the plasma in the coil and the hypertonic bath solution, since the loss per hour decreases somewhat in the later hours of the dialysis. The third major source for fluid loss is urine formation. The last 2 sources of loss are reflected in a slow loss of weight of the animal over the course of the experiment. This is easily obviated by maintaining a stable weight with an intravenous infusion. For experimental purposes the infusion can be stopped, and any degree of dehydration can be superimposed on the electrolyte pattern maintained by the concentration of the artificial kidney bath.

A total of 51 dogs were studied by this method. Eighteen of these were treated as

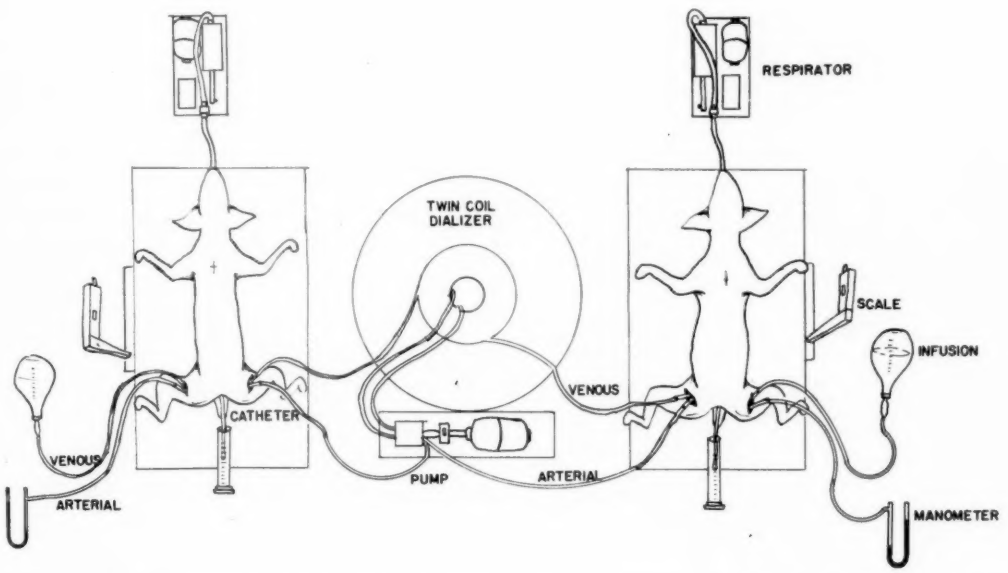

Fig. 1. The experimental setup used. In essence, the extracellular fluids of the dog have been increased by the volume of the extracorporeal system, an added 100 L. Once the extracellular compartment of the dog is in equilibrium with the concentration of solutes in the bath, the level of concentration is very stable, and, despite maximal effort on the part of the kidney or other mechanisms of compensation, the level of hyperosmolality is maintained in the animals dialyzed against hyperosmolar fluids.

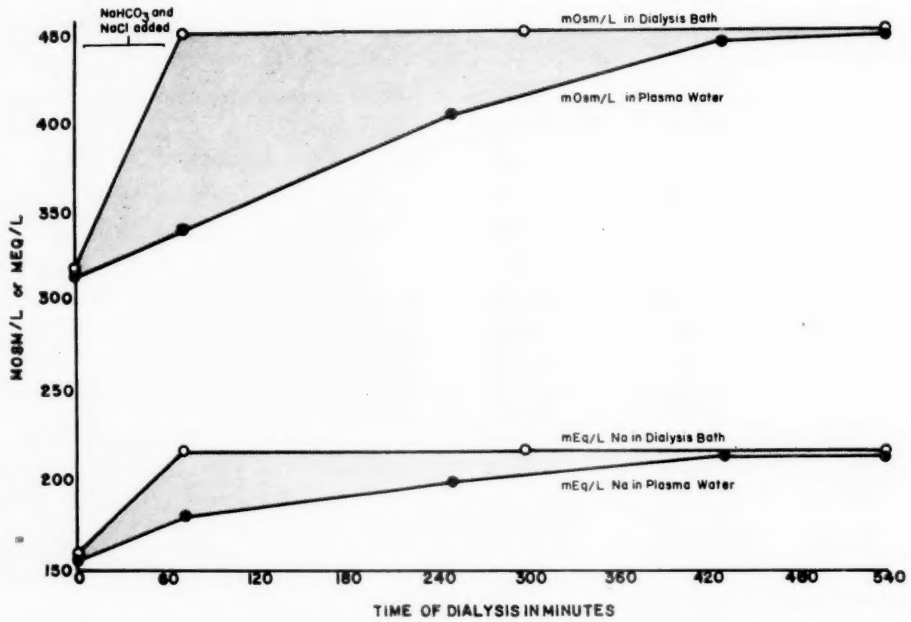

Fig. 2. Diagram illustrates the increase of osmolality and sodium concentration in the plasma water, compared to the concentrations in the dialysate solution. More solute was added in the first hour. Concentrations in the dialysate solution and plasma water were in near equilibrium by the end of the fourth hour after the addition of solute.

controls and dialyzed against the normal bath. Twenty-seven were dialyzed against the normal bath initially, and then sodium chloride and sodium bicarbonate were added gradually over a 1-hour period to the bath to raise the concentration of sodium to 205 mEq. per liter and of chloride to 165 mEq. per liter. The total osmolality was thus raised from 315 to 430 miliosmols per kilogram of water. The animals were dialyzed against this bath for from 5 to 8 hours. In 6 additional animals the concentration of electrolytes in the bath was left unchanged, but the osmolality was raised to 415 milliosmols per kilogram by the addition of urea to the bath.

Microscopic examination of tissue was carried out in 20 dogs. Eight of the dogs were dialyzed against the hypernatremic bath. Seven of the dogs were dialyzed against the control bath and 5 were dialyzed against the urea bath. Of the 8 animals dialyzed against the hyponatremic bath, all were dialyzed in pairs, as previously described. One animal of each pair was maintained at a constant weight, and the other was allowed to become somewhat dehydrated, to the extent of 5 to 8 per cent of its body weight, in order to better duplicate the conditions of clinical hypernatremic dehydration.

RESULTS

After the addition of sodium chloride and sodium bicarbonate to the control bath to raise the concentrations of sodium and chloride, the sodium and chloride levels in the plasma of the dogs rose rapidly to approach the concentration in the bath. This is illustrated in Fig. 2. With allowance for the Donnan factor, the concentration of electrolytes in the plasma water of the dog approaches closely the concentration of electrolytes in the bath over the period of the dialysis. With the increasing concentration of electrolyte and osmolality in the plasma of the dogs, urinary excretion increased markedly in animals maintained at a constant weight. While urinary volume increased, sodium concentration in the urine dropped markedly until it reached a level at or below plasma levels of sodium. In animals in which dehydration was superimposed

on hypernatremia, sodium concentration in the urine likewise fell, though not so far, and urine volume was concomitantly reduced. These and other renal functional changes will be discussed elsewhere.[8]

At autopsy the most striking gross findings were extensive subdural and subarachnoid hemorrhages over the cortex of the brain. These varied in size, but were usually quite extensive, often involving an entire hemisphere. The brain was noted to be shrunken, often contracted 1 cm. or more away from the overlying bone. This shrinking of the brain was noted in all animals with hypernatremia. In 7 of the 8 animals with hypernatremia, moderate to marked hemorrhages were found.

In the animals dialyzed against the control bath, no hemorrhages were found and the brain appeared to be of normal size. In the animals dialyzed against the hyperosmolar urea bath, the brains also showed some shrinkage, although this seemed to be of a lesser degree than that found in the hypernatremic animals. Subdural and arachnoid hemorrhages were not found in the brains of any of the 5 uremic dogs, although in one the brain was somewhat hyperemic. Another gross pathologic finding in both the hypernatremic and uremic dogs was multiple petechiae scattered over the parietal and visceral peritoneum. These also occurred occasionally in the control dogs, although to a much lesser degree.

Microscopic evidence of renal tubular necrosis was found in 6 of the 8 hypernatremic dogs. This was characterized (Fig. 3) by intensely eosinophilic, granular alteration of epithelial cells of the convoluted tubules, certainly proximal and possibly distal. The nuclei of these cells showed striking karyorrhexis. The latter seemed to occur first since it was often present before evident alteration of the cytoplasm.

An additional change (Fig. 4) was seen in 4 hypernatremic animals with and one without frank epithelial cell necrosis. Large, poorly defined vacuoles collected in the basal part of the convoluted tubular epithelial cells adjacent to their nuclei. In the most extreme development of this change, cleavage occurred at this level, so that the major distal portions of adjacent cells were cast into the lumen in sheets, leaving occasional nuclei and cytoplasmic shreds adherent to the basement membrane. Even a modicum of caution makes us regard this striking alteration as an artefact. We believe, however,

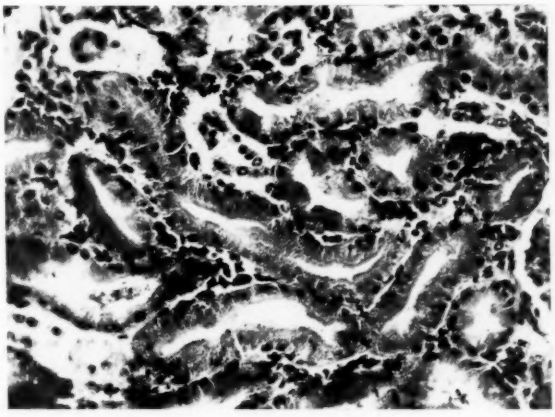

Fig. 3. Photomicrograph shows the acute tubular necrosis which occurred in one of the dogs made hypernatremic. The period of hypernatremia was 6 hours, with the maximum hypernatremia maintained over the last 2 hours. The marked disintegration of tubular cells is readily apparent in the tubules in the center. Granularity, loss of cellular detail, and pyknotic and fragmented nuclei are seen. (×350; reduced 4/11.)

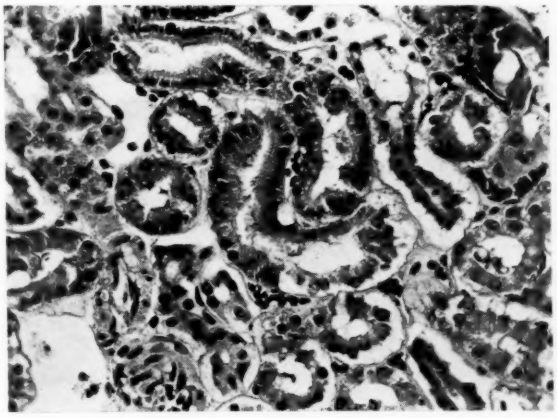

Fig. 4. Photomicrograph of sections of renal tissue from another dog with hypernatremia. Again marked necrosis of tubular cells is seen with pyknotic and fragmented nuclei and granular disintegrating cytoplasm. Vacuolation of tubular cells is clearly seen. (×350; reduced 4/11.)

that this may be an artefact which is preconditioned by an unusual intravital collection of fluid in the basal segments of the convoluted epithelial cells. Thus, 7 of the 8 animals showed some pathologic change within the tubular cells. The glomeruli of all of the kidneys appeared normal and without evidence of acute pathologic change on hematoxylin and eosin staining after formalin fixation.

It was interesting to note that the glomerular filtration rate, as reflected by the creatinine clearance, remained unchanged during the course of the experiment. None of the changes described were observed in any of the animals of the control series or in any of the animals in the urea series. In addition, the kidneys of 6 normal dogs, sacrificed for other reasons in the laboratory, were examined as an additional control group. In none of these animals were the changes described found.

DISCUSSION

The results suggest that the clinical finding of renal failure and acute tubular necrosis in patients with hypernatremia may be related to the electrolyte disturbance itself. In the experimental animals of this study, the renal lesions induced in the animals which were normovolemic and hypernatremic were of approximately the same degree and type as in those which were hypovolemic and hypernatremic. Thus the entire group of 8 animals has been considered as a single group, and it is believed that the renal changes were due primarily to the increased sodium and chloride concentration of the extracellular fluid. These ions which are excluded from the interior of the cell bear the chief responsibility for the distribution of water on either side of the cell membrane. When an increase in extracellular osmolality of an equivalent degree was created by a diffusable osmol such as urea, no lesions were induced in the tubular cells. This suggests that the cellular damage was due to a marked increase in osmolality by effectively nondiffusible, or only partly diffusible, ions on one side of the cell membrane. The intracellular necrosis observed might be related to a marked intracellular dehydration as water was drawn out of the cell by the hyperosmotic extracellular fluids. It has been suggested by some[8] that there are also alterations in the chemical anatomy within the cell which produce "idiogenic osmols." The changes in chemical anatomy may represent a prenecrotic stage of cellular desiccation.

The significance of the vacuolation seen in the tubular cells is unknown, but this change appears to be related to the hypernatremic state, since it was not found in the controls, the urea treated animals, or in the untreated dogs. The gross hemorrhages found in the subdural and subarachnoid spaces of the hypernatremic dogs duplicate similar lesions found clinically in hypernatremic infants,[13] and experimentally in cats and rats made hypernatremic by intraperitoneal injections of saline and urea solutions.[14] It is likely that evidence of acute tubular necrosis found in patients with hypernatremia may be related, at least in part, to the hypernatremia per se, as well as to other complicating clinical factors.

The clinical implications of these findings are clear. Hypernatremia in the range of 200 milliosmols per liter may be lethal, through the induction of severe cellular damage to the brain and kidneys. This damage, once it has occurred, is not immediately reparable simply by returning the electrolyte balance to normal. Once the presence of hypernatremia has been discovered in a patient every effort should be made to return electrolyte balance to normal and avoid cellular damage. In the presence of severe hypernatremia, the urine produced is frequently of low osmolality and renal excretion of salt is low. Thus urinary excretion is not only unable to correct the sodium imbalance, but may actually make it worse. The only source for correction of this state is the intake of exogenous water. This would seem to be best provided by infusions of 5 per cent dextrose in water, although therapy must be individualized in accordance with the nature of the whole physiologic disturbance. At the

some time, the factors which led the patient to his hypernatremic state must be corrected, if possible.

SUMMARY AND CONCLUSIONS

With an artificial kidney, a steady state of severe hypernatremia of approximately 200 mEq. per liter was created in 8 dogs for periods of 5 to 8 hours. In 4 of these animals body water volume was held constant. In 5 animals, by the same technique, hyperosmolality without hypernatremia was created by the use of urea. Seven animals were dialyzed on the artificial kidney against a bath of normal electrolyte composition. The last 2 groups of animals served as controls for the first group.

Subarachnoid and subdural hemorrhages occurred in 7 of the 8 hypernatremic dogs. These changes did not occur in the urea-treated dogs, or in the dogs dialyzed against a normal bath.

Seven of the 8 hypernatremic dogs showed changes in the renal tubular epithelium. These changes consisted of scattered areas of acute tubular necrosis in the proximal and distal tubules. Several animals demonstrated an accompanying finding of large vacuoles in the tubular cells. The glomerular capillaries showed no change. No changes were seen in the renal tubules of the control animals or the urea-treated animals.

Severe degrees of hypernatremia, without accompanying circulatory disturbance, can induce definite histologic damage in the cerebral and renal tissues. It would not be expected that these changes, once they occur, could be corrected by returning the electrolyte pattern to normal.

The authors wish to acknowledge the assistance of Dr. Abou D. Pollack in reviewing and interpreting the histologic material.

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Experimental wound infections: contamination versus surgical technique

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It is customary in some quarters to attribute wound infections primarily to faults of asepsis. It is also widely believed that the incidence of wound infection depends in some degree on the surgical competence with which the wound is handled. We have attempted to clarify this problem by asking, "Will wounds regularly tolerate heavy contamination without becoming infected if surgical technique is otherwise strictly in accord with certain recognized principles?" An experiment based on this question was designed to test various aspects of wound closure in dogs in the presence of heavy contamination with cultures of staphylococci obtained from infected wounds.

METHODS

The dogs were anesthetized with pentobarbital. Bilateral transverse wounds were made through the abdominal wall, with standard aseptic technique. A few dogs in preliminary experiments had 3 or 4 wounds. The external and internal oblique muscles were cut, as was a portion of the rectus. The wounds were 5 to 10 cm. long, depending on size of the animal. Ligatures of No. 4-0 chromic catgut were used for hemostasis. The peritoneum and transverse layer were closed together with a running suture before contamination.

A trial group of experiments showed that interrupted cutaneous sutures nearly always became infected superficially while a continuous subcuticular suture did not. The latter type was used in all subsequent experiments. Other procedures to be studied differed on the two sides.

The contaminating staphylococci were hemolytic, coagulase positive, and phage type 53-75-77, a pattern found in some human surgical wound infections. The original culture came from a patient's infected wound and subsequent cultures were obtained from the wounds of experimental animals. No stock cultures were kept in vitro for more than 1 month. Preliminary experiments in dogs showed that a subcutaneous injection of 800 million bacteria regularly produced abscesses. Bacterial counts were carried out on all contaminating cultures and showed 80 million to 800 million staphylococci in each 2.5 ml. Virulence of the material was verified by the fact that every culture produced some wound infections. Wounds were contaminated by instillation of 2.5 ml. of fluid from a broth culture. After contamination, wounds were covered with a gauze sponge and left undisturbed for from 5 to 15 minutes. Some preliminary work was done with purulent discharge from wounds infected with staphylococci. This was used in place of the broth culture and invariably caused a severe reaction and early breakdown of the wound. Cultures were used in the experiments reported subsequently, When wounds were irrigated, a total of 250 ml. of saline solution

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Table I. *Comparison of 4-layer with 7-layer closure of contaminated wounds*

Closure	*No. of wounds*	*No. infected*
4-layer	12	11
7-layer	12	3

Table II. *Comparison of No. 4-0 monofilament nylon with No. 4-0 braided silk in closure of contaminated wounds*

Suture	*No. of wounds*	*No. infected*
Silk	12	10
Nylon	12	4

was used. All visible clot and debris was flushed from crevices before closure of the next layer.

Wounds were evaluated by daily inspection, by culture, and by studies of multiple cross sections after the animals had been sacrificed. Infections for the most part were obvious, but occasionally there was only a drop or two of serous drainage. If this material drained for 2 days the wound was considered infected. Fluctuation without discharge was also observed and classed as an infection. All such wounds gave a pure culture of the original staphylococci. Open wounds, on the other hand, showed the presence of micro-aerophilic streptococci and other organisms in addition to staphylococci.

RESULTS

Our total experience in 96 dogs is analyzed with respect to the significance of natural resistance to staphylococcal infection in the experimental animals. Eighty-eight per cent of the animals had at least 1 wound infection and 70 per cent of wounds were infected. In 31 of the 96 dogs, wound infections were unilateral. In this group, at least, it is possible that natural resistance or susceptibility did not predominate over the technical factor being studied. In some of the remaining animals there were significant differences in severity of lesions between the two sides, even though both were infected. This will be be brought out in the description of individual experiments.

The first experiment concerned with the problem of the potential dead space. One wound was closed in 4 accurately matched layers with a running suture of No. 5-0 nylon passed through the fascia or muscle at 3 mm. intervals, about 3 mm. from the edge. No attempt was made to obliterate the potential spaces between layers. The scanty subcutaneous tissue was not separately sutured. In the other wound, 7 layers were sutured, including the subcutaneous tissues. The fasciae of either side of the internal and external oblique muscles were sutured separately, and sutures included the subjacent layer in such a way that all potential dead space was nearly obliterated. All wounds were washed beginning 5 minutes after they were contaminated. Closure took approximately 1 hour, even after some experience. The side with 7 layers was more indurated than the other when the operation was completed. Table I shows data from 12 dogs. The 3 infections of the 7-layer closure were minimal. On the 4-layer side, 2 wounds completely separated, 4 had a large amount of drainage, and 5 remained fluctuant without drainage for a period of 3 to 7 days. An example of the appearance of these wounds is shown in Fig. 1. Cross sections of the wounds showed occasional small pockets in the subcutaneous tissue of the 7-layer wounds. Dead spaces were noted throughout the layers on the 4-layer side and these often extended the entire length of the wound.

Table III. *Comparison of No. 4-0 braided Dacron with No. 4-0 braided silk in closure of contaminated wounds*

Suture	*No. of wounds*	*No. infected*
Dacron	12	11
Silk	12	12

Table IV. *Effect of washing contaminated wounds with 250 ml. of saline solution during closure*

Treatment	*No. of wounds*	*No. infected*
Washing	12	9
None	12	10

There were 8 wounds that showed no evidence of infection, though the presence of infected wounds on the opposite sides of the same animals established their susceptibility.

In a second experiment nylon and silk sutures were compared (Table II). All wounds were closed with No. 4-0 suture in 5 layers with each layer being sutured to the one beneath. (Note that in the 4-layer closures in the previous experiment the layers were not approximated to each other.) In 4 nylon-sutured wounds there was minimal infection. The silk-sutured wounds showed complete separation in 3 cases and considerable discharge in the other 7. In these wounds the difference in inflammatory response (Fig. 2) was also noted on all cross sections of the two types of wounds, except in 2 dogs which had complete healing of both wounds.

After observation of the probable superiority of monofilament nylon, the question arose as to whether composition of structure of the sutures was responsible for the difference. Since braided nylon was not available, No. 4-0 braided Dacron was compared with No. 4-0 silk. Data in Table III show that there was no difference in the results with the 2 types of suture.

The effect of washing with 250 ml. of saline solution beginning 15 minutes after contamination was also studied. Bilateral wounds were treated in an identical fashion except for the washing of 1 wound. A 5-layer closure was made with No. 4-0 nylon. Contamination consisted of a dose of approximately 800 million bacteria.

Data in Table IV show no decrease in the incidence of infection with this amount of washing. Two dogs had complete healing of both wounds. Cross sections of wounds showed little difference in the two wound types. This experiment is not directly comparable with the other, because of heavier contamination and longer waiting period before washing.

DISCUSSION

The complete obliteration of the dead space involves considerable increase in suture

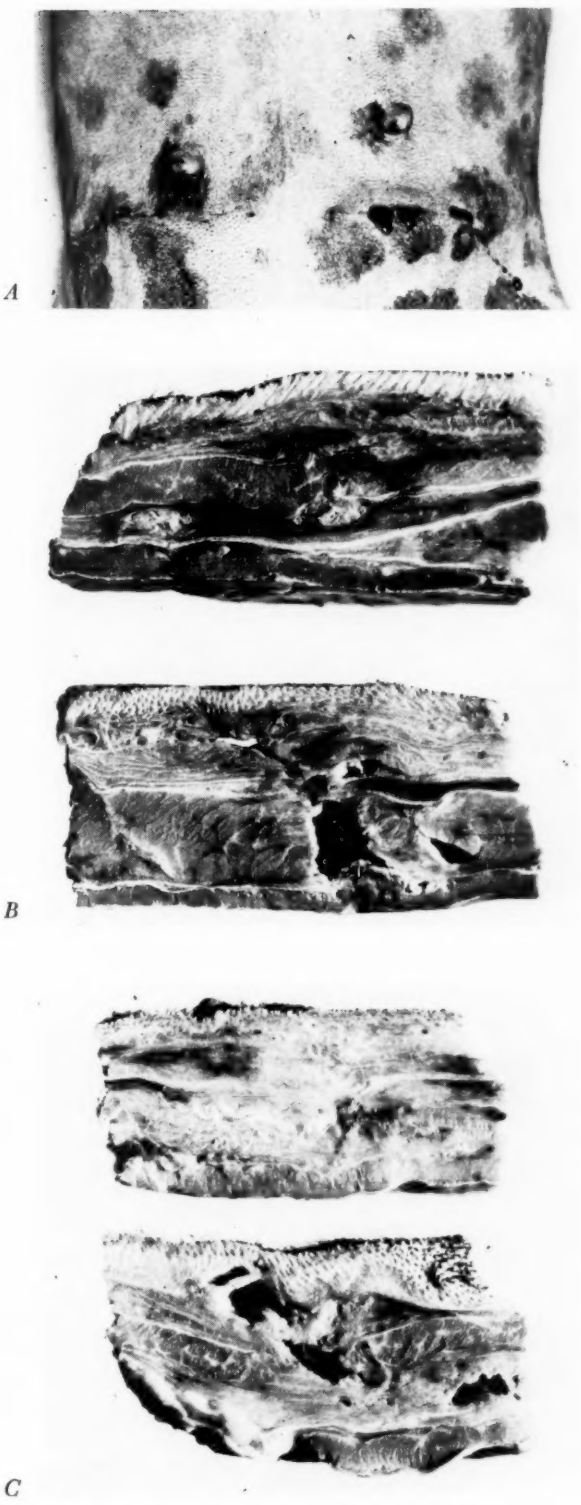

Fig. 1. *A,* The appearance of the 7-layer (left side) and draining 4-layer wounds on the fourth postoperative day. *B,* A cross section of wounds which was made on the fifth postoperative day. The upper section is the 7-layer closure. *C,* Similar sections which were taken from another animal on the sixth postoperative day.

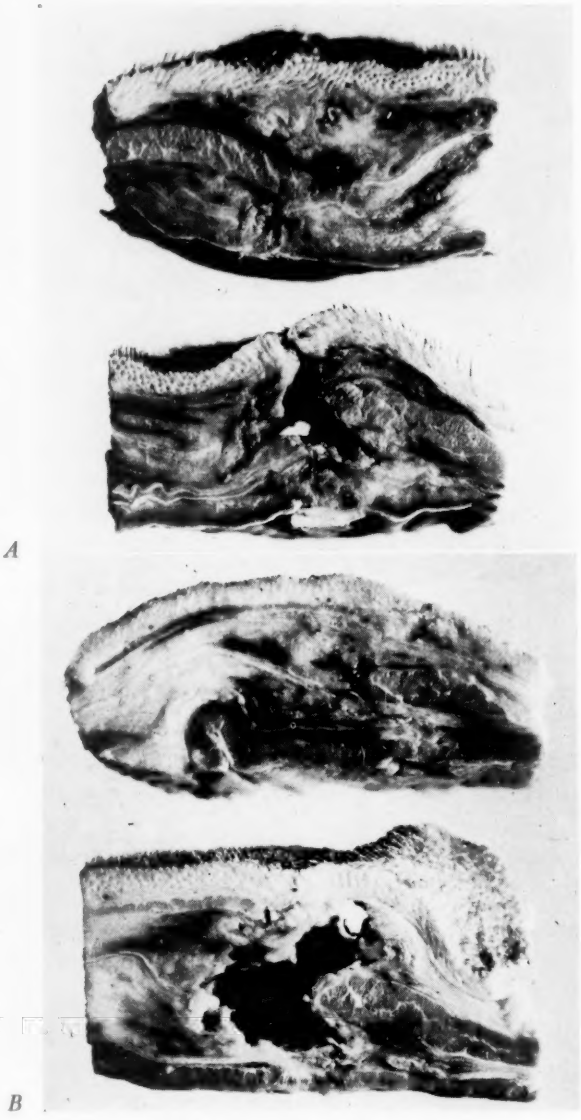

Fig. 2. *A*, Cross sections of wounds closed with nylon (top) and silk (bottom) on the eighth postoperative day. *B*, Similar sections from another animal on the seventh postoperative day.

material and more trauma to the tissues in the placement of sutures. Therefore, the extent to which this practice is desirable is questionable. Experimental results indicated that the increased amount of suture material and trauma was of less consequence than potential dead space in the genesis of wound infections. Thus, one item of surgical technique, the painstaking obliteration by suture of all potential dead space, appreciably reduced the occurrence of wound infections in the presence of virulent contamination.

At the same time, the use of braided sutures (whether silk or Dacron) in heavily contaminated wounds was once again shown to be deleterious, and success with the 7-layer closure was undoubtedly due in part to use of monofilament nylon. Elek[1] estimated that silk suture in a wound enhances the virulence of staphylococci by a factor of 10,000. The use of monofilament nylon in general surgery has been relatively infrequent, partly because of difficulties with knotting such slippery material. If additional evidence substantiates the apparent benignity of nylon as a running suture, even in the presence of infection, it may find considerable use clinically in that form. It is stronger, smoother, and more durable than catgut, and is easier to handle than wire.

In the experiments with washing wounds, we found no consistent effect. However, there is no doubt that washing removes both the bacteria and the blood clot, dead tissue, and so forth, on which they grow. It may be assumed that either more thorough washing or less heavy contamination might have brought out a difference, as it has in other experiments.[2] In all our groups, contamination was far in excess of anything that could occur in normal operations with clean wounds.

Surgical technique in relation to wound healing can be guided by a single principle —the assurance of maximum blood supply to all healing tissue. Concordance with this principle implies elimination of actual or potential dead space and accurate matching of tissue layers, so that all cells are directly nourished from both sides of the wound. It implies minimal ligature and suture material, devitalized tissue, and hematoma in the wound. It implies all that is technically necessary for uncomplicated wound healing, except for asepsis. The principle of asepsis, at least with respect to staphylococci, seems to be necessary in proportion with neglect of the other principle. Of course no one would willingly do without the additional safeguard of asepsis, however perfect his technique. Nevertheless, the occurrence of a staphylococcal wound infection seems more

likely to be a reflection of poor technique than of unusual contamination.

CONCLUSIONS

1. In experimental wounds contaminated by staphylococci maximum attention to obliteration of potential dead spaces by suture reduces the likelihood of infection.

2. Monofilament nylon as a continuous suture is preferable to braided Dacron or silk in these wounds.

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Prolonged hypothermia below 25° C. for periods over 20 hours: influence of therapy and technique on survival

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The use of hypothermia as a clinical and experimental adjunct has received much attention in the past 2 decades. Although short-term hypothermia of a few hours' duration has been the subject of most observations and has received the most clinical use, prolonged hypothermia has been investigated intermittently.

The first notable clinical use of prolonged hypothermia was reported by Smith and Fay[25] in 1939 and was applied to the treatment of cancer. In 1941, schizophrenic patients were treated by prolonged refrigeration by Dill and Forbes[6] and Talbott.[27] In 1951, Laufman[18] reported the survival of a woman exposed to –7° C. for approximately 11 hours after a heavy consumption of alcohol; body temperature was 16° C. In 1953 and 1954, Horvath's group[16, 26] reported survival in a few dogs after 20 hours of body temperature below 25° C. In 1955, Fisher and associates[12] evaluated this problem and later made additional observations on metabolic changes,[9] pathologic and histochemical changes,[8] and cardiovascular changes[7] of dogs subjected to body temperatures below 25° C. Even by 12 hours at this temperature, serious physiologic changes and a formidable mortality rate were observed. In 1957, Gray[14] cooled dogs for 72 hours at body temperatures between 26° and 30° C. and observed that the few animals which survived rewarming never regained consciousness. In 1958, MacPhee and Gray[22] reaffirmed these findings.

Most investigators who use prolonged hypothermia have sounded warnings of its dangers. Yet, there are many aspects of the problem which have not been thoroughly explored. The use of an efficient automatic respirator, proper positioning of the subject during the hypothermic period, and the effect of various therapies on survival have not been investigated. It is still not certain whether the time limits of hypothermia are contingent more on the inherent limitations of the subject or on the methods of inducing and maintaining it. The hibernator is living proof that cold is not harmful to mammals over long periods.

We have studied prolonged hypothermia for several reasons. First, it has clinical usefulness as a treatment for gravely ill, febrile patients.[19] Second, the effect of hypothermia in protecting against lethal radiation dosages[1, 15] combined with its elimination of the need for food and water may make this the ideal modality for space travel. Third, body temperatures lower than Smith and Fay[25] were able to achieve, maintained over a prolonged time, may be more beneficial in the treatment of cancer. Fourth, a thorough investigation of prolonged hypothermia would magnify any inherent dangers of short-term

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hypothermia and, by focusing attention on these danger points, would make this frequently used clinical adjunct even safer.

METHODS AND MATERIALS

Ninety-eight mongrel dogs which weighed from 8 to 18 kilograms were studied. Anesthesia was induced by thiopental sodium, or pentobarbital sodium, 30 mg. per kilogram, with additional increments of pentobarbital sodium, thiopental sodium, or ether given as needed during the induction of hypothermia. After intubation, the dog was connected to an open-system mechanical respirator with a respiratory mixture either of room air or of 5 per cent carbon dioxide and 95 per cent oxygen. The femoral artery and vein were then cannulated and cooling was induced by wrapping in a rubber refrigeration blanket which was connected to a cooling machine. In the earlier experiments, a standard Therm-O-Rite* machine was preset to keep a constant temperature of 22° to 24° C., while in later experiments, an Autotherm† cooling apparatus was used. The latter was preset to the desired body temperature and automatically cooled or heated, depending on the reading of the electrical thermistor thermometer inserted in the dog's esophagus. It was accurate in keeping the body temperature within 0.5° C. of the preset temperature. All dogs were kept at body temperatures below 25° C. for 20 hours or longer. Cooling to 25° C. took 2.5 to 3 hours and rewarming to 35° C. approximately the same time.

Mean blood pressure was read directly from an aneroid manometer attached to the femoral artery cannula, while venous pressure was read directly from a saline manometer calibrated in centimeters of water and attached to the cannula in the femoral vein. Blood samples drawn for hematocrits from the arterial line were centrifuged for 30 minutes at 3,000 r.p.m. in Wintrobe tubes. Determinations of pH from arterial and venous samples were read from a Beckman model G pH meter (an anaerobic determination with external blood electrodes). The reading was corrected to the body temperature of the animal at the time of sampling. Serum sodium and potassium were determined by the Beckman flame photometer. Arterial and venous carbon dioxide and blood oxygen content and capacity were measured by a Van Slyke apparatus with the manometric method.

Blood and plasma volume determinations were carried out with Evans blue dye. This was injected into the femoral vein and removed 10 minutes later from the femoral artery. Electrocardiographic recordings were made with the Sanborn Poly-Viso machine. Autopsies were performed on all animals. Histologic sections from the liver, kidney, adrenal glands, lung, spleen, and intestine were taken from several animals with hematoxylin and eosin staining technique.

Twelve groups of dogs were studied. Dogs in Groups I through X had intermittent positive-pressure respiration of 15 to 20 mm. Hg while lying on their side. Group I included 9 dogs which received no medication or fluids. Group II included 12 dogs that had no medication or fluids but had a respiratory mixture of 5 per cent carbon dioxide and 95 per cent oxygen. Group III was composed of 11 dogs that received 800 ml. of saline solution or Ringer's lactate during the hypothermic period. Two of these received respiratory mixture of 5 per cent carbon dioxide and 95 per cent oxygen. Group IV included 18 dogs that received 1 to 10 mg. per kilogram of heparin in 500 ml. of saline solution or Ringer's lactate. In 7 of these the 5 per cent carbon dioxide mixture was used. Group V was composed of 6 dogs that had partial exsanguination of 200 to 400 ml. of blood 1 week prior to cooling. Group VI was composed of 4 dogs which were subjected to splenectomy 2 weeks prior to cooling and given the 5 per cent carbon dioxide mixture during cooling. Group VII was composed of 5 dogs which received a continuous drip of 40 to 80 mg. of Vasoxyl, a sympathomimetic agent, in 800

*Therm-O-Rite Products Corp., 17 Main Street, Buffalo, N. Y.

†Autotherm Corp., P.O. Box 25122, West Los Angeles 25, Calif.

ml. of saline solution during the hypothermic period. Group VIII was composed of 7 dogs which received 150 to 300 mg. of chlorpromazine and quantities of saline solution up to 2,000 ml. during the hypothermic period. Group IX was composed of 7 dogs which received Dibenzylene, a sympatholytic agent, 0.5 to 1.0 mg. per kilogram in 300 ml. of saline solution prior to and during cooling. Group X consisted of 7 dogs that received cortisone, 15 mg. per kilogram 4 times a day for the 4 days before cooling.

Dogs in Groups XI and XII had intermittent positive-pressure respiration, less than 12 mm. Hg, with an inspiratory-expiratory ratio of 1 to 5, and were cooled while in a prone position. The prevention of shivering by deep anesthesia during induction of hypothermia was a prominent feature, and the trachea was frequently aspirated during rewarming. Group XI was composed of 5 dogs which received 0.05 to 0.25 mg. per kilogram of reserpine, a hypotensive agent, before cooling. Sodium bicarbonate, 25 mEq., was given prior to rewarming. Group XII was composed of 7 dogs that received the same treatment as Group XI except for omission of reserpine.

RESULTS

Cold narcosis. During the hypothermic period, additional anesthesia was not needed. The critical temperature was slightly different for each dog but tended to be approximately 22° to 24° C. Below this temperature, the dog would remain quiet and immobile with no shivering for the entire hypothermic period. If this critical temperature was exceeded by even 0.5° C., the dog would shiver slightly and make swallowing movements. These motions would cease when the temperature was again lowered. During the hypothermic period the pupils were pin point and nonreactive to light and the nictitating membrane was frequently drawn across the eye.

Survival. Of the 98 dogs studied, 54 (55 per cent) survived the 20-hour period of hypothermia. The dangers of rewarming were amply illustrated by the subsequent fate of 23 of these dogs which died during rewarming to 35° C. This left only 31 (32 per cent) of the 98 dogs that survived all phases of prolonged hypothermia. The subsequent fate of these 31 dogs deserves comment. A few never regained full consciousness and evidenced uncoordinated movements. In early experiments, hind-leg paralysis was noted in a few dogs. Thirteen (42 per cent) of the 31 survivors died within 24 hours after rewarming to 35° C., 3 (9 per cent) died within 48 hours, 2 (7 per cent) died within 1 week, and only 13 of the 31 survived indefinitely with no demonstrable sequelae.

The survival results in each of the 12 groups are presented in Table I. Statistical analysis of these groups by the chi-square method showed only 2 groups that had significantly increased survival rates compared to the controls in Group I. In both of the groups, shivering was carefully prevented by multiple frequent injections of pentobarbital; in both, the prone position rather than a lateral position was used, and the trachea was frequently aspirated. In addition, both received sodium bicarbonate prior to rewarming. The 5 dogs in Group XI, which received reserpine in addition to the changes in technique, all survived rewarming ($p = 0.0001$). Five of the 7 dogs in Group XII in which reserpine was omitted also survived rewarming to 35° C. ($p = 0.046$). Since these 2 groups did not differ significantly from each other, the possible value of reserpine cannot be commented upon with such small groups, and the increased survival appears to be due to the changes in technique which both groups received.

Although results in the groups in which Dibenzylene or carbon dioxide was used were somewhat better than the control results, the differences were not significant. The use of saline solution, heparin, partial exsanguination, prior splenectomy, or chlorpromazine did not affect ultimate survival in any fashion. The use of Vasoxyl or cortisone, however, was attended by a consistent mortality rate.

To determine whether any of the therapies

Table I. *Survival after hypothermia below 25° C. for 20 hours*

Groups	*Survivors*	*Died during rewarming*	*Died during hypothermia*	*Total*
I. Controls	2	1	6	9
II. Carbon dioxide	6	2	4	12
III. Saline	2	5	4	11
IV. Heparin	4	7	7	18
V. Exsanguination	2	1	3	6
VI. Splenectomy	1	2	1	4
VII. Vasoxyl	–	–	5	5
VIII. Chlorpromazine	1	2	4	7
IX. Dibenzylene	3	1	3	7
X. Cortisone	–	1	6	7
XI. Reserpine and technical changes	5	–	–	5
XII. Technical changes	5	1	1	7
All dogs	31 (32%)	23 (23%)	44 (45%)	98

mentioned might have been effective in keeping the dog alive during the 20-hour hypothermic period, though not during rewarming, the data were rearranged to include as survivors all those that lived until rewarming began. As can be seen from Table I, the addition of dogs which died during rewarming to the survivor columns resulted in a more substantial survival rate, especially with saline, heparin, and prior splenectomy. In none, however, except Groups XI and XII, was there a significant difference in comparison to the controls. Therefore, even during the hypothermic period alone, only the previously mentioned changes in technique and possibly the addition of reserpine were significant factors in increasing survival rate.

Hematocrit. The 79 dogs in which hematocrits were studied showed a definite, constant, progressive increase in hematocrit. The average per cent increase at 4 hours in all dogs was 19.5 per cent; at 12 hours this increased to 30.8 per cent; and by 20 hours it had increased to 53.6 per cent. During rewarming, at approximately 30° C., the hematocrit dropped slightly to an increase of 51 per cent. The difference in per cent increase of hematocrit between survivors and dogs which died during cooling or rewarming is shown graphically in Fig. 1. The survivors had a smaller rise than nonsurvivors. At 4 hours, while the increase was only 11.4 per cent in the survivors, it was 24.5 per cent in the dogs which died during rewarming ($p = 0.0102$). At 12 hours, a similar disparity existed with survivors having a 24.6 per cent increase and dogs which died during rewarming a 39.2 per cent increase ($p = 0.0375$). At 20 hours the gap was even greater—46.4 per cent and 69 per cent, respectively ($p = 0.0131$). Dogs that died during the hypothermic period had a middle course, and did not differ statistically from survivors or dogs which died during rewarming.

During rewarming, while the survivors' hematocrit tended to stay at the same level, dogs which died during rewarming showed a progressive increase to 82 per cent. Measurements were made in only 3 of the latter and the difference was not statistically significant. The initial hematocrit reading was of no prognostic value as related to survival. In general, these changes in hematocrit are consistent with the findings of Fisher's group[10, 11] in dogs subjected to prolonged hypothermia. Even natural hibernators were shown to have a rise in hematocrit during the hibernation period.[21]

Plasma volume. Plasma volume studied in 13 dogs decreased 30.4 per cent by 20 hours. There was no significant correlation with survival, perhaps because of the small number of dogs. D'Amato and Hegnauer[5] have noted a decrease in plasma volume of 12 per cent when dogs were cooled to 20° C. for shorter periods.

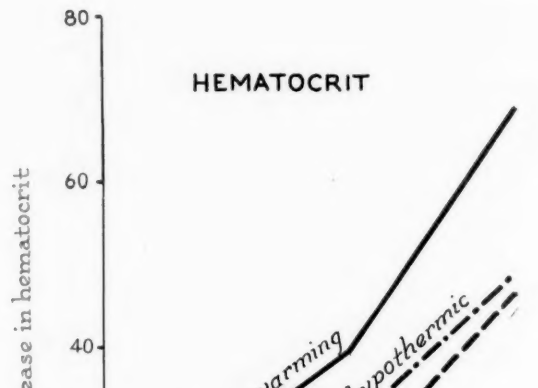

Fig. 1. Changes in hematocrit during prolonged hypothermia.

Heart rate. Changes in heart rate in 34 dogs during the hypothermic period are illustrated in Fig. 2. There was no significant correlation between changes in heart rate and survival.

Blood pressure. The average changes in arterial pressure in 68 dogs are also shown in Fig. 2. By 4 hours the arterial pressure had decreased to 70 mm. Hg and by 20 hours there was a further small drop to 65 mm. Hg. With Vasoxyl and cortisone, these decreases in blood pressure were avoided and the arterial pressure was maintained. However, this artificially elevated pressure seemed to have a deleterious effect, as it was associated with a 100 per cent mortality rate. Fig. 3 shows a comparison of arterial pressure changes between dogs given Vasoxyl and those given cortisone and between survivors and dogs which died during cooling and rewarming. It can clearly be seen that there is a tendency for the arterial pressure of survivors to increase slightly over the 4-hour value while dogs that die become more hypotensive. At 20 hours the difference in arterial pressure between survivors and dogs which died during rewarming ($p = 0.0088$) and survivors and dogs which died during hypothermia ($p = 0.0193$) is significant. Venous pressures showed no consistent changes and tended to remain at precooling values.

pH. The changes encountered in arterial pH differed considerably depending upon whether the respiratory mixture was room air or 5 per cent carbon dioxide in oxygen. The average initial pH was quite low in all dogs—7.25 in dogs given carbon dioxide and 7.32 in those given air.

Fig. 4 shows a comparison of the average changes during the hypothermic period in all dogs given room air and carbon dioxide. The general pattern in both is the same. The dogs respired with room air had a sharp rise to 7.51, probably due to hyperventilation, and then a tapering-off to 7.39 at 20 hours with no severe acidosis. In the dogs respired with 5 per cent carbon dioxide in oxygen, however, there is a slight increase to 7.29 at 4 hours, and by 12 hours this dropped to 7.15 and remained at this low level at 20 hours. There was no significant correlation found between changes in pH and survival.

The trend, then, in prolonged hypothermia, appears to be one of relatively increasing acidosis in comparison to the earlier values. Fisher[12] also found an acidosis, but the drop in pH occurred in the early hours and was not progressive. However, the dogs he studied were breathing spontaneously while the dogs in this study had artificial respiration which may have deferred the onset of the acidosis.

Carbon dioxide content. In one dog given a 5 per cent carbon dioxide in oxygen respiratory mixture, the carbon dioxide content remained at 50 vol. per cent throughout the entire period. The 7 dogs respired with room air had a lower initial value of 30 vol. per cent and remained at that level throughout the hypothermic period. There was no correlation between carbon dioxide content and survival. Fisher,[12] however, noted a drop in carbon dioxide content.

Carbon dioxide tension. In 8 dogs studied for changes in carbon dioxide tension, fairly constant levels were noted throughout the hypothermic period. There were higher constant levels when a carbon dioxide respiratory mixture was used. Again, no correlation with survival was found.

Oxygen saturation. The arterial and venous oxygen saturation was studied in 9 dogs. The average arterial oxygen saturation never changed appreciably and remained about 93 per cent during the hypothermic and rewarming periods. Fig. 5 illustrates the profound changes which occurred in venous saturation. Though rising above the initial value to 91 per cent at 4 hours, it had dropped to 35 per cent by 20 hours, and during rewarming dropped further to 30 per cent. These changes from initial values were statistically significant, both at 20 hours and during rewarming ($p = <0.0001$). There was no difference between survivors and nonsurvivors in this respect.

Decrease in content of venous oxygen was noted by Fisher and associates[11] to begin by 14 hours, probably secondary to the decrease in cardiac output. The stagnant anoxemia and marked increase in coefficient of oxygen utilization which result from decreased cardiac output evidently decrease the venous oxygen content.

Plasma hemoglobin. Twenty-seven dogs were studied for changes in plasma hemoglobin. The average initial value for all dogs was 27 mg. per cent; by 20 hours it had increased to 145 mg. per cent. Fig. 6 shows a comparison of the increases in survivors with those in dogs which died during cooling and rewarming. The greatest increase occurred in the survivors and the least in the dogs which died during hypothermia. There was a significant difference between the former and

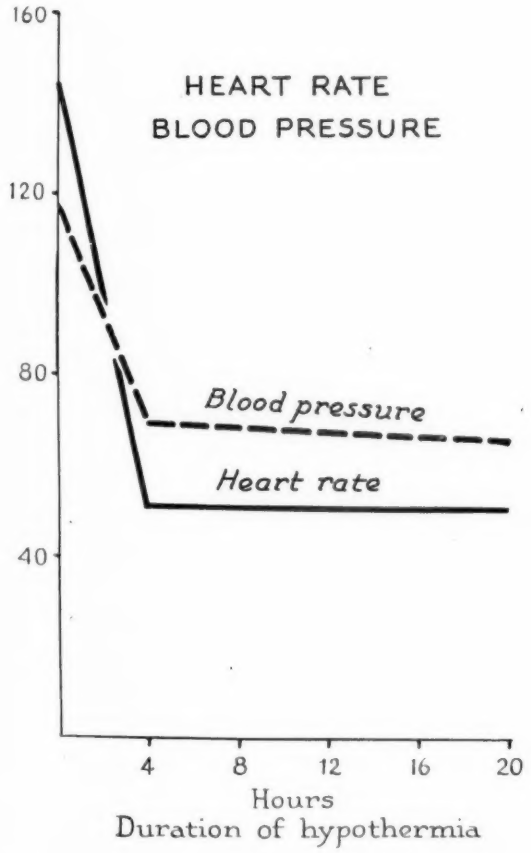

Fig. 2. Heart rate and arterial pressure during prolonged hypothermia.

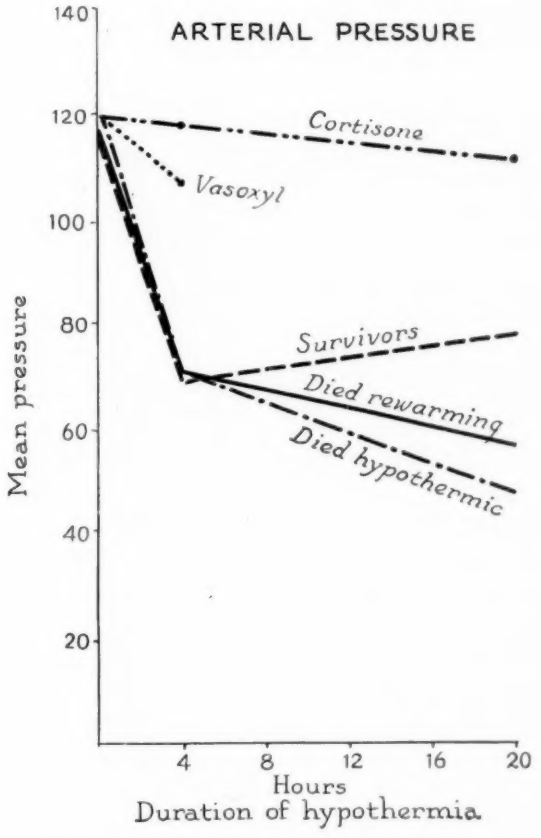

Fig. 3. Relation of arterial pressure to survival in prolonged hypothermia.

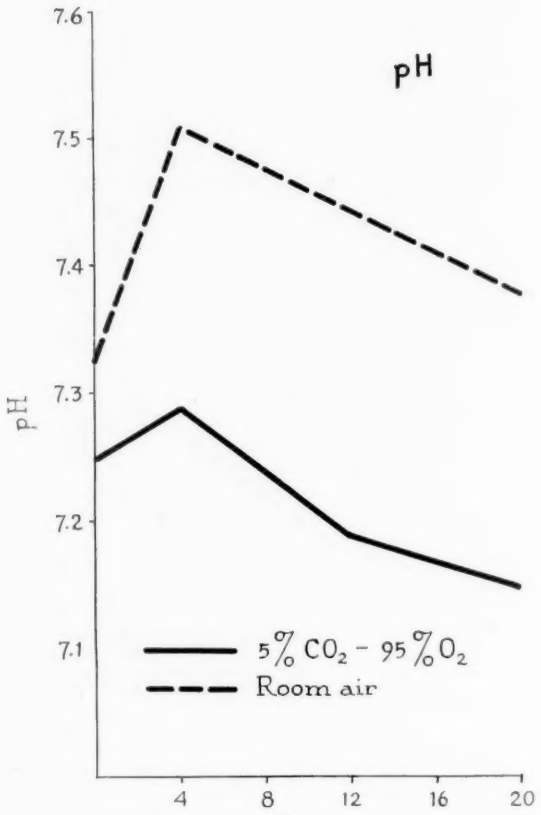

Fig. 4. Arterial pH with room air and carbon dioxide respiration during prolonged hypothermia.

the latter ($p = 0.0203$) and between dogs which died during rewarming and those which died during hypothermia ($p = < 0.0001$). It may be that the hemolysis occurs in all dogs but is less apparent in those that die in the cooling period because their circulation is impaired so markedly that it cannot reabsorb the hemolyzed blood from a sequestered site.

Electrolytes. Studies on sodium and potassium were performed only in 4 dogs. No changes from initial values were noted at 20 hours, a finding similar to that of Fisher and colleagues.[12]

Electrocardiogram. With progressive cooling the electrocardiogram showed gradual development of a sinus tachycardia with some prolongation of the P-R interval and QRS complex and lengthening of the Q-T segment, though findings were variable in most dogs. In addition, other changes not ordinarily associated with a slow rate were seen in the S-T segment and in the T-wave, which became diphasic and then deeply and bizarrely inverted as body temperature was lowered. Sometimes these changes did not appear until after relatively long periods of hypothermia.

The presence of a secondary wave which closely followed the ventricular complex and frequently impinged upon it was seen in some tracings. Boba[3] stated that a definite correlation exists between the appearance of this wave and the incidence of ventricular fibrillation. This wave was observed in these studies frequently in animals that subsequently died. In agreement with Fisher and his group, however, this wave cannot be interpreted uniformly as an ominous sign of impending ventricular fibrillation, since it was also seen in some survivors.

Pathology. Autopsy in dogs which died during the experiment showed varying degrees of congestion and hemorrhage of the bowel mucosa. These changes were frequently seen in survivors which died within 24 hours, but were not seen in survivors sacrificed later than this. Petecchial hemorrhages were found in subendothelial layers of the ventricles in the heart. Scarring from these lesions was occasionally seen in dogs which survived. Sarajas[23] has commented on the frequency of this finding after hypothermia. Pulmonary changes varied, animals which received large amounts of saline solution often showing pulmonary edema. Atelectasis of a lobe was a common finding, and on several occasions both lungs were atelectatic and were the main cause of death within 24 hours of rewarming. The liver was frequently congested and often appeared somewhat friable. No other gross findings were frequent or typical. Microscopic sections from a few animals showed congestion of the liver, spleen, and intestine. A slight vacuolation of hepatic central zone cells was seen in some animals.

DISCUSSION

The physiologic effects of prolonged hypothermia are not trivial. A state of somnolence similar to deep anesthesia is present at low

temperatures. The changes in hematocrit are profound and consistent and are correlated with survival. The decreased plasma volume further reflects the hemoconcentration present. The decreased heart rate and arterial pressure may not necessarily represent physiologic impairment, but perhaps physiologic alterations requisite for the needs of the body. An early low arterial pressure is compatible with survival as long as further decreases do not occur during the hypothermic period. Artificial methods of elevating it to a normothermic level are associated with a consistently high mortality rate. Except for the tendency of the pH to become relatively more acid during hypothermia, other indices of acid-base balance such as carbon dioxide tension and carbon dioxide content do not change with the increased duration of hypothermia.

The decreased oxygen saturation, however, may indicate a detrimental feature of prolonged cooling. Increasing cardiac output to prevent stagnant anoxemia could prevent this. On the other hand, survivors also have uniformly shown low venous oxygen saturation, and its importance is not clear. Electrolytes are not appreciably altered. The electrocardiogram shows no consistent significant changes which can be attributed to cold, except for its reflection of bradycardia at these temperatures.

In Lillihei's[20] investigation of endotoxin shock, a listing of the ensuing physiologic changes almost duplicates the changes found in this study of prolonged hypothermia. There is a decrease in plasma volume, the hematocrit increases, and the plasma hemoglobin increases. When the animal died from irreversible shock, it had congestion and hemorrhagic necrosis of the bowel and a congested liver. Even the subendothelial hemorrhages in the ventricles of the heart, which Sarajas[23] associates with hypothermia, were found in the animal which died in irreversible shock. Furthermore, the changes are not limited to endotoxin shock, but are found in irreversible hemorrhagic shock and chronic epinephrine shock.[13, 20] These pathologic findings are almost identical to what

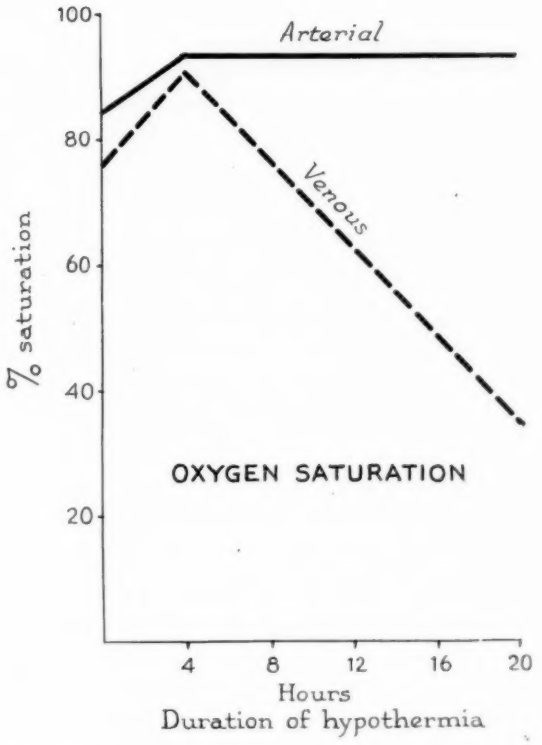

Fig. 5. Changes in oxygen saturation during prolonged hypothermia.

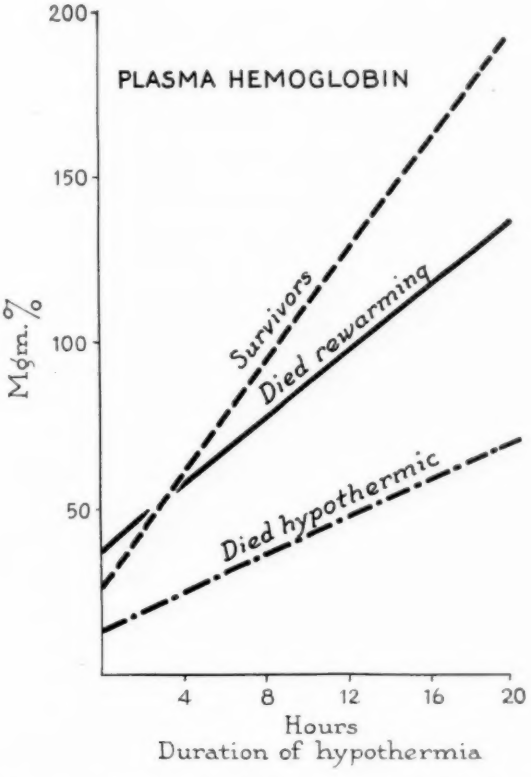

Fig. 6. Relation of plasma hemoglobin levels to survival during prolonged hypothermia.

is observed in the animals which die in prolonged hypothermia.

A look at the only 2 groups in which survival significantly increased in comparison to survival in the control group may shed some light on the cause of death. In Groups XI and XII, several conditions differed from those in the previous 10 groups. The control of shivering, the adoption of the prone position, the administration of sodium bicarbonate immediately prior to rewarming, the careful tracheal aspiration during rewarming, and the use of the short inspiratory phase and low pressure intermittent positive-pressure respiration are factors difficult to evaluate. The fact that these 2 groups did not differ significantly in survival from each other infers that the variation in techniques may be more pertinent than the addition of reserpine. The failure of chlorpromazine- and Dibenzylene-treated dogs to have a significantly higher survival rate also lends support to the importance of technical changes.

Whether or not it is important to control shivering during induction of hypothermia is a subject that has received much attention. If one is trying to achieve imitation of hibernators, no shivering should be allowed. The hibernator cools to 5° C. with no shivering, but uses shivering extensively as a major source of heat production in awakening and regaining normal body temperature.[21] Shivering during induction of hypothermia is not harmless. It has been noted to increase venous pressure. It also increases oxygen consumption, markedly if violent[6, 11] and slightly if it is only a fine tremor.[2] It depletes glycogen in the liver,[4, 6] probably through the release of epinephrine. Exactly the opposite occurs in hibernators, which have no depletion of liver glycogen during cooling but do have depletion of liver glycogen during arousal.[4] If, in addition to shivering, the animal is partially awake because of inadequate anesthesia during induction, it struggles violently with dilated pupils and increased respiration. This emotional response is an adequate stimulus for the increased secretion of norepinephrine.[13]

The selective depression of sympathoadrenal stimulation during induction of hypothermia may be extremely important. Whether or not there is any stress reaction during exposure to cold and hypothermia is a controversial point. Hume,[17] in measuring secretion of corticoids and catecholamines in the adrenal vein, found no increase in the anesthetized or unanesthetized animal. However, others have reported histologic evidence of stress during hypothermia. Even more pertinent to this study, pentobarbital was found to selectively depress this stress reaction in comparison to ether or nitrous oxide.[24] The lethal effects of administration of norepinephrine during endotoxin shock,[20] and the uniform mortality rate that occurred in the present study when Vasoxyl was administered, tend to bear out the concept of the pernicious effects of sympathoadrenal stimulation.

The failure of Dibenzylene to increase survival rate significantly is difficult to explain, but these dogs received none of the ancillary changes in technique enumerated for the last 2 groups. The consistent mortality rate noted when cortisone was used is also inexplicable at present. The dogs treated with chlorpromazine received up to 2,000 ml. of saline solution, and many died of pulmonary edema. Consequently, an adequate trial of chlorpromazine alone cannot be commented upon.

From these studies we can conclude that definite physiologic changes are related directly to the duration of hypothermia below 25° C. The encouraging survival rates noted with the addition of the techniques described certainly demand further investigation. Although prolonged hypothermia may still be the ideal modality for space travel, as well as a desirable technique to evaluate in the treatment of carcinoma, its present dangerous status would preclude any present clinical application without additional study.

SUMMARY

In this study, we have tried to evaluate the physiologic alterations which occur in prolonged hypothermia and the effect of technique and therapy upon survival. Several features, such as the control of shiver-

ing during induction and the use of the prone position seem to be important technical details. The use of 5 per cent carbon dioxide in oxygen as a respiratory mixture, splenectomy, saline solution, partial exsanguination, chlorpromazine, heparin, or Dibenzylene did not significantly increase survival over that of the controls. The use of Vasoxyl or cortisone was attended by a uniform mortality rate. Treatment with reserpine was followed by consistent survival, but control dogs with similar changes in technique of cooling also had a high survival rate, which suggests that the change in technique may be more important than the addition of reserpine. In its present state of development, prolonged hypothermia below 25° C. is too dangerous to recommend for clinical use without further study.

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The coating of intravascular plastic prostheses with colloidal graphite

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At the present time there are several types of prosthetic valves that are available for placement in the canine and human heart. Most of these valves are constructed of plastic with the cusp, flap, or ball valve principle used in their design. Many of these prosthetic units have been evaluated in mechanical valve testers over long periods of time and appear to be extremely satisfactory from a hemodynamic and functional standpoint; however, their successful use in the canine and human heart has been markedly impeded by the very serious problem of thrombus formation on the valve unit. At the recent Public Health Symposium "Prosthetic Valves for Cardiac Surgery," there were only a few reported cases of long-term survival of dogs after placement of valvular prostheses.[2, 4-6] In almost every instance, dogs that survived the immediate postoperative period soon died as a result of thrombosis on the prosthesis. Valve design and valve material did not seem to alter these results in the canine heart. Ross and associates[7] studied clotting on plastic probes in the superior vena cava of the dog, and found that all plastics tested were the site of thrombus formation within 30 minutes. Even with Teflon there was moderate clot formation after 22 minutes. Frater and Ellis[2] found that all types of valves, constructed of several different plastics, clotted after insertion in the canine heart. The clotting seemed to occur even in the presence of prolonged heparinization. Kolff[4] reported equally discouraging results. He noted the occurrence of thrombi on several types of plastic valves and intracardiac plastic patches even while systemic fibrinolysin was used. Muller and Littlefield[6] reported the experience at the University of Virginia with a Teflon fabric cusp valve in the aortic area. The valve was placed in 50 animals and there were no long-term survivals. Long and his group[5] reported the experience at the University of Minnesota with a bicuspid silastic valve in the mitral and tricuspid area. This valve was placed in 25 dogs and the longest survival was 19 days. Again clotting was a serious problem. Many other investigators have had equally discouraging results in canine studies. Although it is generally agreed that clot formation on valve prostheses is not as serious a factor in the human heart, the severity of the problem in the canine heart has made it very difficult to adequately evaluate valve designs prior to clinical use.

At the University of Wisconsin many different valve designs have been evaluated. We have had the greatest experience, however, with a flap valve constructed of a rigid

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plastic housing and a flexible butterfly-wing leaflet. This type of valve performs well in the pulse duplicator, opens with a minimum of pressure, and produces no measurable pressure gradient across the valve. This valve has been constructed of several different thermoplastic materials and in almost every instance thrombosis on the prosthesis has led to early death of the dog.

In an attempt to find a more satisfactory material for valve prostheses, the authors initiated a study of the clot-producing characteristics of several plastic materials and coating substances. It was believed that a severe test of clot prevention would be the placement of a prosthesis in the venous stream in a manner similar to that employed by Ross.[7] Rather than placing plastic probes in the vena cava as Ross did, we elected to utilize tubular plastic rings which were somewhat analogous to the rigid valve housing used for the flap valve. It was decided to construct these rings of several different rigid plastic materials and also to coat some of them with substances that might aid in clot prevention. We also elected to evaluate the factor of electric charge as related to clot formation on the plastic rings.

It has long been known that white blood cells, red blood cells, fibrinogen, and other protein components of the blood are negatively charged at the normal pH of blood. In an electrophoretic cell, Abramson[1] was able to demonstrate that the white blood cells migrate to the positive pole of the cell. It was also shown that washed platelets migrate to the positive pole of an electrophoretic cell. In 1953 Sawyer and colleagues[8, 9] demonstrated that the normal potential difference across a blood vessel wall was 1 to 5 mv. with the blood or intima relatively negative with respect to the adventitia. These authors reported that injury to the intima altered the normal potential difference and when the transmural polarity was reversed, making the blood or intima relatively positive with respect to the adventitia, thrombosis frequently occurred. More recently, several additional studies have been reported which show the influence of electric charge on clotting in blood vessels. Williams, and his group[12] demonstrated that if negatively and positively charged platinum electrodes were externally placed on opposite sides of the canine jugular vein, a moderate clot developed on the vein wall nearest the positive electrode (5 Ma. current for 1 hour). Long-term studies with a low voltage circuit led these authors to conclude that it was tissue damage from current flow rather than regional electropositivity that caused the thrombosis. Schwartz,[11] in a similar study of intravascular clotting, observed that clotting occurred in an occluded femoral vein enclosed in a positively charged platinum sheath but not in a vein enclosed in a negatively charged platinum sheath. Heparin prevented clotting from occurring within the positive field, and dicumarol did not offer this protection. The difference in effectiveness of the two drugs was partially attributed to the extreme negative charge of heparin. Sawyer and associates[10] studied the effects of small electrical currents on clotting in the mesenteric vessels of the rat and noted that thrombosis seemed to occur first on the vessel wall nearest the positive electrode. With regard to intravascular prostheses, it has been noted that an epicardial-endocardial electrode placed in the canine heart for chronic heart block was usually free of clot when the endocardial plate carried the negative charge.[3] Also, Ross and colleagues,[7] in evaluating the clot formation on different plastics and other substances, believed that the best results were obtained with coatings of sulfonated or sulfated polysaccharides which possessed a high negative charge.

The evidence of the several investigators mentioned seems to indicate a significant relationship between electrical charge and intravascular clotting. Although the present study was originally planned as an investigation of the clot propagating properties of plastic materials, it was believed that this would afford a good opportunity to further evaluate the factor of electrical charge as related to clotting on intravascular prostheses.

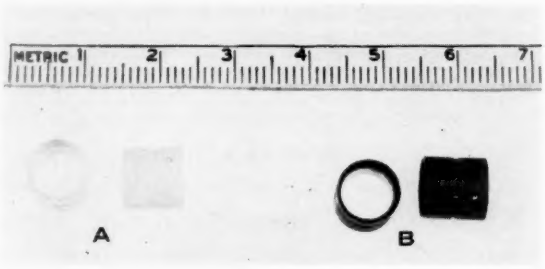

Fig. 1. *A*, A pair of Kel-F rings which show design and size of the plastic rings used in this study. *B*, Plastic rings coated with colloidal graphite.

METHODS

Rigid plastic rings were designed with a 7 mm. internal diameter and a 0.5 mm. wall thickness. The rings were 8 mm. long and had sharp leading and trailing edges (Fig. 1, *A*). All rings were molded except for those of methyl methacrylate and tetrafluoroethylene (Teflon) which were machined from a rod stock and highly polished. This was necessary because of difficulty in molding satisfactory rings of the latter 2 plastics. Rings of acetal (Delrin), polycarbonate (Lexan), polypropylene, both intermediate and high density polyethylene, and trifluorochloroethylene (Kel-F) were injection-molded in suitable dies. Polyvinyl chloride rings were also molded with a rigid plastisol formulation by modified injection techniques. Polyurethane and silicone rubber, which have been used in making flexible valve constructions and leaflets, were not tested because we were principally interested in materials suitable for rigid valve housings.

A siliconized surface was tested, however, by coating methyl methacrylate rings with Dow Corning silicone No. 200 (350 centistrokes viscosity). This is a silicone solution designed for application to plastic and was baked on at 130° F.

Methyl methacrylate rings were also coated with conductive colloidal graphite* (Fig. 1, *B*.) In 1 series of 5 rings the graphite was painted on the methyl methacrylate; however, brush application left several tiny uncoated areas. A second series of 5 methyl methacrylate rings were therefore dipped in a graphite solution and evaluated for clot propagation. It was found that the ideal solution for dip-coating was a colloidal graphite solution diluted 3 to 1 with 95 per cent ethanol. This solution was thin enough to permit dipping yet appeared to provide an adequate coating of graphite. Each ring was initially dipped in plain ethanol for the purpose of cleaning and pretreating the plastic surface. This permitted a better bond between the plastic and the colloidal graphite. Some rings were dipped 2 or 3 times in the graphite solution for a better coating. Most of the rings were placed in a forced-draft oven at 130° F. for 72 hours in order to remove all diluting solvents.

In another series of graphite-coated rings, an insulated wire was connected to the prosthesis (Fig. 2) so that an electrical charge could be applied by use of a dry cell battery.

Healthy dogs which weighed 7 to 10 kilograms were anesthetized with Nembutal and placed on a respirator which utilized compressed air. A right thoracotomy was performed through the fifth intercostal space, the superior and inferior venae cavae were carefully dissected from surrounding tissue, and tapes were passed around these vessels as far from the heart as possible. A purse-string suture was placed in the right atrial wall. With very short periods of inflow stasis, a plastic ring was inserted through a right atriotomy into one of the exposed caval vessels and immediately wrapped with a piece of Teflon fabric. The Teflon fabric was placed around the vein so that there was no cul-de-sac between the prosthesis and vein wall. There was virtually no discrepancy in size between the plastic rings and the venae cavae in animals of this weight range. The rings were examined at 1 hour and rings with a patent lumen were placed back in the vena cava and examined again at the end of 2 hours. Each vena cava was utilized for the testing of only 1 prosthetic ring and there was no apparent difference in clotting between the superior and inferior venae

*Dag 154 colloidal graphite manufactured by the Acheson Colloids Company, Port Huron, Mich.

cavae. Systemic anticoagulation was not used; however, the rings were rinsed initially in a dilute solution of heparinized saline in order to minimize clotting during the placement with inflow stasis.

The wired graphite rings were placed in the superior vena cava and the wire connected to 1 pole of a 9 V. nickel cadmium battery. A 2,200 ohm resistor was placed in series with the battery and the circuit completed by placement of a wire between the battery and the latissimus dorsi (Fig. 2). Voltages across the resistor and the conductive graphite ring were approximately 6 and 3 V., respectively, with the average current being 3 Ma. The wired rings were evaluated with both a positive charge and a negative charge. Five rings of each of the plastics and coatings were placed in the vena cava for evaluation.

RESULTS

The data on clot formation in the different types of rings are depicted in Figs. 3 and 4. The clot in each ring is depicted diagrammatically.

Uncoated plastic rings. It may be noted that all of the Delrin rings were completely clotted within 1 hour. Rings of Lexan, polyvinyl chloride, polypropylene, and medium density polyethylene were severely clotted in 1 hour and all of these rings were completely occluded at the end of 2 hours. High density polyethylene and Kel-F rings provided the best results of all the uncoated plastic prostheses tested. In each of the last 2 groups, 1 ring was clotted at 1 hour and a second ring was clotted or almost clotted after 2 hours. All of the Teflon rings were severely clotted after 2 hours in the vena cava.

Silicone-coated methyl methacrylate rings. A silicone coating on the highly polished, machined rings of methyl methacrylate significantly improved the clot-repelling qualities of these rings, as might be expected. We were surprised to observe, however, that 1 ring was completely occluded and a second ring was nearly occluded after 2 hours in the vena cava (Figs. 3 and 5).

Graphite-coated methyl methacrylate rings (brush application). Four of the 5 methyl methacrylate rings painted with colloidal graphite were relatively clean after a

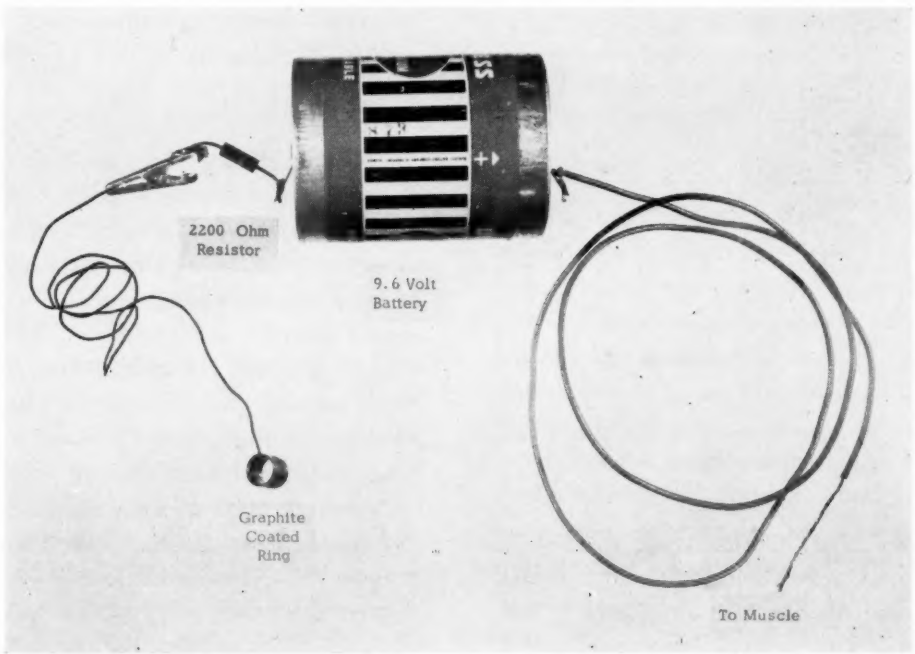

Fig. 2. The technique for application of a small electric charge to the surface of a graphite-coated plastic ring.

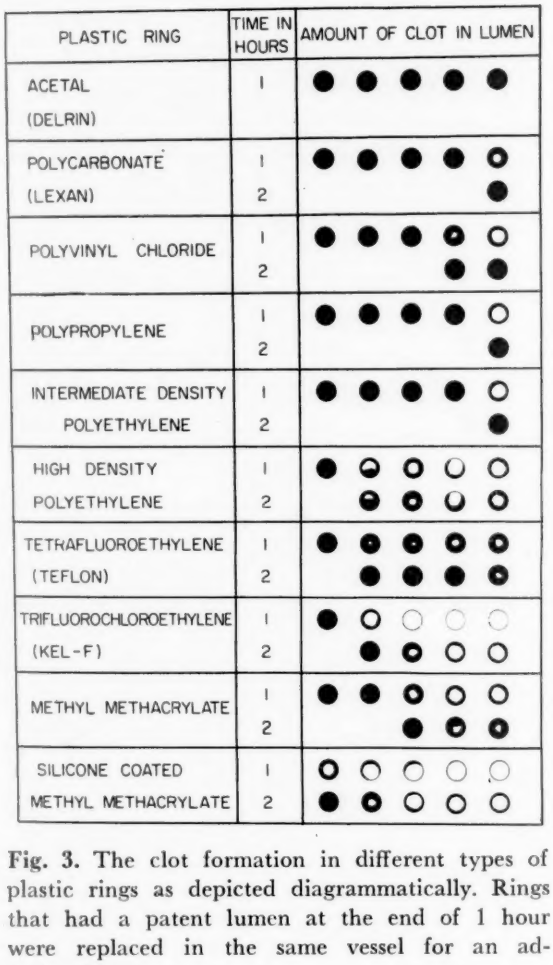

Fig. 3. The clot formation in different types of plastic rings as depicted diagrammatically. Rings that had a patent lumen at the end of 1 hour were replaced in the same vessel for an additional hour.

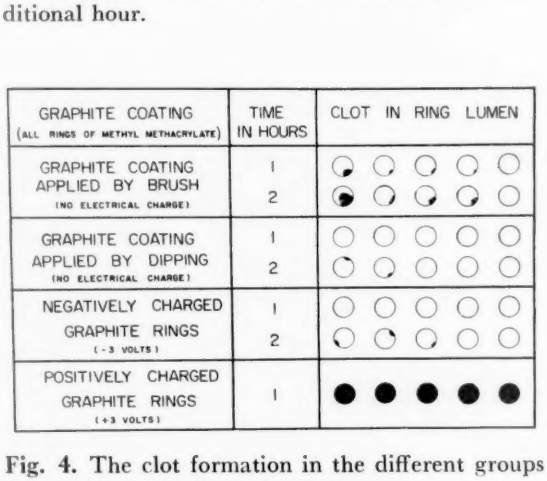
GRAPHITE COATING (ALL RINGS OF METHYL METHACRYLATE)
TIME IN HOURS
CLOT IN RING LUMEN
GRAPHITE COATING APPLIED BY BRUSH (NO ELECTRICAL CHARGE)
GRAPHITE COATING APPLIED BY DIPPING (NO ELECTRICAL CHARGE)
NEGATIVELY CHARGED GRAPHITE RINGS (-3 VOLTS)
POSITIVELY CHARGED GRAPHITE RINGS (+3 VOLTS)

Fig. 4. The clot formation in the different groups of graphite-coated plastic rings.

2-hour placement in the vena cava. The fifth ring had a moderate clot at 2 hours. This was one of the first rings which had been painted with colloidal graphite, and it was interesting to note that the clot originated from a small area of methyl methacrylate which was not coated with graphite. The clear area was the result of a brush mark. Care was then taken to cover the methyl methacrylate rings as thoroughly as possible with graphite, but in 3 rings there were tiny clots which originated from minute, clear areas of methyl methacrylate. The fifth ring was completely clean at 2 hours.

Graphite-coated methyl methacrylate rings (dip application). In order to obviate the occurrence of microscopic and macroscopic clear areas that resulted from brush marks, 5 rings were dipped in a diluted colloidal graphite solution. All 5 rings were completely clean at 1 hour and 2 rings had 0.5 mm. particles of thrombus at 2 hours (Figs. 4 and 6). Three rings which had been dipped in graphite were completely clean after 2 hours in the vena cava.

Graphite-coated methyl methacrylate rings with electrical charge. Five graphite-coated rings with a negative charge of approximately 3 V. were as free of clot as rings without a charge. Five graphite-coated rings with a positive charge of approximately 3 V. were completely clotted within 1 hour. Pressure recordings in the jugular vein during some of the latter experiments showed complete thrombotic occlusion within 30 minutes.

DISCUSSION

The placement of a prosthesis in the vena cava is an extremely severe test for any plastic material. The poor results obtained with the plastic rings in our study need not incriminate these materials for use in prosthetic valves in a high velocity blood stream. It was believed, however, that this type of study would provide information on the relative clot-repelling ability of different plastic materials and coating substances.

A comparative analysis of the pure plastic rings indicates that Kel-F and high density polyethylene resisted clotting to a better degree than any of the other plastics. It is possible that molded (as opposed to machined) Teflon rings would have performed as well as or better than Kel-F rings be-

cause of the close similarity of these plastics; however, we found that Kel-F was much easier to mold than Teflon and provided extremely clean castings. The silicone coating certainly improved the performance of the methyl methacrylate rings, as might be anticipated.

The data obtained on the graphite-coated rings, with and without small electrical charges, are particularly interesting. At the inception of the study it was believed that a graphite coating with a negative charge might offer some protection against clotting. We were encouraged, therefore, to observe that the negatively charged graphite rings were extremely clean after 2 hours in the venous stream. It was of interest also that the positively charged rings had severe clot formation in less than 1 hour, and the clots were much more firmly attached than those which occurred in the lumina of the pure plastic rings. It is obviously not desirable to connect a wire and a battery to an intracardiac prosthetic valve unit in order to prevent the formation of thrombus. There could be interference with myocardial conduction and other readily apparent problems. We were pleased to note, therefore, that the graphite-dipped rings without an externally applied negative charge were also relatively free of clot after 2 hours in the vena cava.

Colloidal graphite was chosen as the conductive coating for this study because it could be easily applied to a flexible or hard plastic prosthesis. Graphite is elemental carbon in the form of laminar hexagonal crystals. It is a nonmetallic conductor and has been used extensively in electrical circuits. In the colloidal form (Dag 154), extremely fine particles of graphite are suspended in a vehicle which consists mainly of isopropyl alcohol. The particles are separated for the most part as crystal aggregates and the mass mean particle size is between 1 and 2 μ. There are a very few flocculant particles present, ranging in size up to 8 μ in diameter. When Dag 154 is applied to plastic the solvent evaporates and leaves the graphite crystals in a small amount of cellulosic plastic binder. The graphite adheres very well to most plastics,* forms an extremely smooth surface, and, like Teflon, is slightly waxy to touch. It is the latter quality that has led to the extensive use of graphite as a dry lubricant in industry.

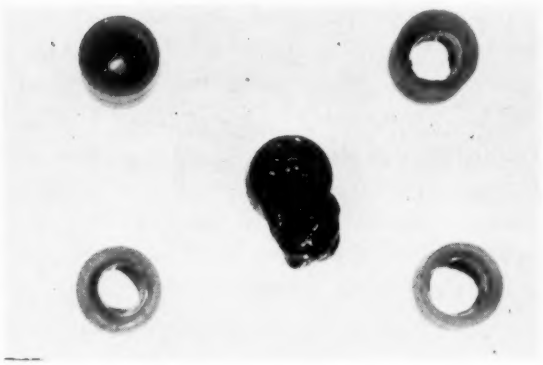

Fig. 5. The clot formation in 5 silicone-coated methyl methacrylate rings. All of these were placed in the vena cava for 2 hours.

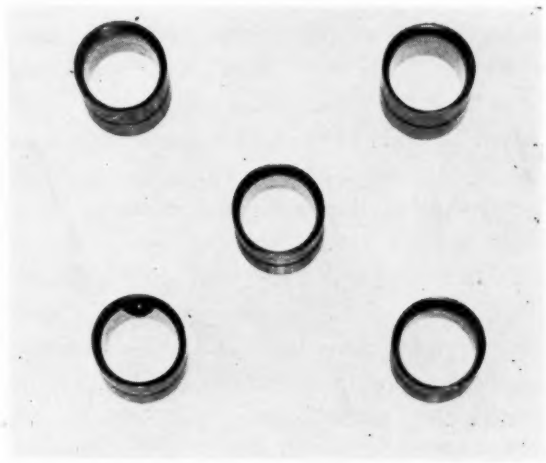

Fig. 6. The appearance of 5 graphite-coated plastic rings after 2-hour placement in the vena cava. The 2 rings on the left have small particles of thrombus on the upper edge.

We believe that the encouraging results obtained with the graphite-coated rings may be related to several factors. The graphite appears to fill in and cover microscopic and macroscopic defects in the plastic and thus provide an extremely smooth

*The colloidal graphite does not adhere well to silicone rubber.

surface. Also, the graphite coating is conductive, which may be of some importance. It is conceivable that a nonconductive prosthesis of plastic material accumulates a positive electrostatic charge as a result of the friction of the negatively charged blood elements flowing over the surface. When a positive static charge builds up on the plastic prosthesis, the negatively charged blood elements are attracted to it with resultant early clot formation. There are several analogous examples of this problem of electrostatic charge in industry and commerce. The friction of the air stream flowing over the surface of an airplane wing permits the accummulation of an electrostatic charge on the wing surface. Because of the hazard of explosion from this electrostatic charge, short segments of sash cord dipped in colloidal graphite are attached to the trailing edge of the wing. The slightly frayed end of the sash cord provides hundreds of fine points for dispersion of the electrostatic charge from the wing surface. Thus, in the case of the graphite-coated rings, it may have been the ability of the conductive graphite crystals to dissipate a positive electrostatic charge that contributed to the successful performance of these rings. Certainly this is only one of several major factors in clot prevention. Chemical reactivity of a foreign surface is of extreme importance in clot formation. Other factors, such as nonwettability of a surface, are of questionable importance.[7] Comparative in vitro studies on wettability and chemical reactivity of graphite and other coating substances are presently being carried out and will be reported in the near future.

Long-term studies of graphite-coated prostheses have not been completed. Several graphite-coated rings have been examined after a 1-week placement in the vena cava and most of these rings are free of clot. Also, several graphite-coated rings have been examined after a 2-month placement in the thoracic aorta. These rings were covered with a thin layer of endothelium and there was no destruction of the graphite surface. There was no adverse reaction around the graphite-coated ring in the blood vessel or in the surrounding tissue. Toxicity tests are now in progress. It is believed that graphite (as elemental carbon) will be well tolerated by the body tissues.

A few graphite-coated flap valves have been placed in the canine heart and at this early date the results are encouraging. Considerable work still has to be done with regard to application of the graphite and its solvents to the thin plastic films used for valve leaflets. There is no problem in the application of colloidal graphite to a rigid plastic valve housing, but some solvents can be detrimental to certain plastic films and care has to be exercised in the coating of these materials. Also, some flexibility is lost when graphite is applied to a plastic film and thinner materials must be used. The use of films of conductive plastic for the flexible leaflet appears promising.

Studies are also progressing on the use of graphite coatings in several additional areas. Teflon grafts have been coated with graphite for replacement of vena caval and small-lumen arterial segments. Results to date in these studies are also encouraging and will be the subject of reports in the future.

CONCLUSIONS

1. Rigid plastic rings were constructed of 9 different plastic materials and placed in the canine vena cava for evaluation of clot formation. With the exception of rings constructed of Kel-F and high density polyethylene, all rings were severely clotted within 2 hours.

2. A silicone coating on methyl methacrylate rings reduced the clot formation on these prostheses very significantly; however, there was severe clotting on 2 of 5 siliconized rings after 2 hours in the vena cava.

3. Methyl methacrylate rings coated with conductive colloidal graphite (by a dipping process) were virtually free of clot after 2 hours in the vena cava. Application of a small negative charge to the conductive graphite surface did not alter these results; however, application of a positive charge to the graphite surface produced a severe

thrombosis within a 1-hour period.

4. It is postulated that satisfactory results were obtained with the graphite-coated rings because this material provides an extremely smooth surface which may dissipate a positive electrostatic charge from the prosthesis. This would minimize the attraction of negatively charged blood elements to the prosthesis.

5. Early results with graphite-coated flap valves and graphite-coated vascular grafts have been encouraging.

The authors wish to thank Dr. Charles W. Crumpton, Director of the McArdle Cardiovascular Laboratories for his assistance and co-operation during the course of this project. We would also like to thank Mr. Francis McMahan, Mr. Mark Mergen, and Mr. Marcus Ravnan for their technical assistance in the performance of these studies, and Dr. Harold J. Dawe and Mr. Arthur J. Stock of the Acheson Colloids Company for supplying technical data on the graphite materials.

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ADDENDUM

Further studies on the colloidal graphite surfaces show some additional factors which may be of value in minimizing clot formation. There may be a very minimal negative charge on the unwired graphite surface which could be of value. We have not been able to measure this directly but some indirect evidence suggests that this is true. A second factor that may play a role in the effectiveness of graphite is the adsorption from the blood stream of heparinlike mucopolysaccharides by the graphite surface. Attempts are presently being made to elute the surface of some of the graphite-coated rings that have been in the vena cava and aorta for several weeks and to try to determine the nature of the eluate. A third factor of questionable importance is the extreme nonwettability of a graphite surface. Additional experience in coating various plastic surfaces shows that the best results are obtained with plastics that are slightly attacked by the diluting solvents in the colloidal graphite. The best coating results to date have been obtained on polycarbonate (Lexan), polyvinyl, and methyl methacrylate.

Effect of hypothermia on blood ammonia formation

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Hypothermia has been suggested as an adjunct to the surgical operation of portacaval shunting in the treatment of acute hemorrhage from esophageal varices.[4, 11] Since one of the sequelae of bleeding into the gastrointestinal tract in patients with cirrhosis of the liver is ammonia intoxication, it seemed important to determine the effect of hypothermia on ammonia formation.

It is well known that bacterial metabolism and growth are temperature dependent. The general effect of increasing temperature upon a given chemical reaction is an increase in the rate of that reaction, and conversely, cooling will, within limits, slow the velocity. Since ammonia is formed mainly by the action of bacterial enzymes within the bowel, it would be expected that both enzymatic action and bacterial growth would be slowed by general hypothermia and if the magnitude of this change is sufficient, then hypothermia might be of clinical value in the treatment of ammonia intoxication in the bleeding cirrhotic patient.

In this study the effect of hypothermia on blood ammonia formation was investigated by determination of the effect of lowering the incubation temperature to 30° C. on fecal cultures and by notation of the effect of general hypothermia on dogs subjected to cooling to 30° C.

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MATERIALS AND METHODS

Determination of effect of temperature change on ammonia production by fecal cultures. Fresh stools were obtained from 3 dogs fed normal kennel rations. The stool specimens were diluted with saline solution 1 to 10 and 0.3 ml. aliquots of this mixture were incubated at 37.5° and 30° C. in closed containers. A total of 28 such aliquots from the saline and fecal mixture were incubated at each temperature. After 60 minutes of incubation, 1.4 ml. of 20 per cent chilled trichloroacetic acid was added to each sample which was then thoroughly mixed and centrifuged. A 0.25 ml. aliquot of the supernatant solution was used for ammonia determination according to the method of Nathan and Rodkey.[9] Zero time was established by the addition of trichloroacetic acid at the time saline solution was added to the fecal mixture.

Investigation of effect of hypothermia on blood ammonia levels of dogs cooled to 30° C. Fourteen dogs were anesthetized with pentobarbital and cooled to 30° C. with cooling blankets. This was accomplished in 2 to 3 hours. Temperatures were measured with an esophageal thermometer. Blood for ammonia determination was taken from the inferior mesenteric vein through a catheter threaded into the small branch of this vein. Care was taken to avoid any obvious congestion of the inferior mesenteric vein. The terminal ileum and low sigmoid colon were ligated in an effort to keep the source

of ammonia relatively constant during the experiment. In 9 of the animals concomitant arterial ammonia levels were measured from the femoral artery. In 6 animals, peripheral venous samples were taken from the femoral vein. The final ammonia level was determined as soon as the temperature fell to 30° C. The ammonia determinations were made by a modification of the Conway method[8] with a 10-minute diffusion time. Because of the possible effect of temperature on diffusion in the Conway technique, the results of this method were compared in 2 dogs in which the method of Nathan and Rodkey[9] was also used. The changes produced by hypothermia appeared consistent with either technique and consequently the Conway method was used for the remainder of the project because of the comparative simplicity of its performance.

Controls were established on 5 dogs which were anesthetized for a similar period of time but were not cooled. Blood was taken from the inferior mesenteric vein and femoral vein and artery in the same manner as in dogs which underwent hypothermia.

Because of the known effect of changes in pH and carbon dioxide tension on blood ammonia levels,[7] pH and carbon dioxide tension in addition to blood ammonia levels were determined in 5 of the dogs subjected to hypothermia. The plasma carbon dioxide was determined according to the method of Van Slyke and Neill[12] and conversion to carbon dioxide tension was made with solubility coefficients and pK changes in reference to temperature.[3]

RESULTS

Determination of temperature coefficient of ammonia production. The reduction in ammonia formation resulting from incubation of the 3 stool specimens at the lower temperature (30° C.) was found to be 88, 64, and 46 per cent, as noted in Table I. The average reduction with combination of all 28 aliquots so incubated at this temperature was 66 per cent. The effect of reduction of the temperature upon the growth rate of bacteria was not measured in this experiment.

Measurement of blood ammonia changes which resulted from cooling to 30° C. The changes in the ammonia content of the inferior mesenteric vein, femoral vein, and femoral artery upon cooling to 30° C. are recorded in Table II. The average ammonia level in the inferior mesenteric vein before cooling was 793 mcg. per cent. This value varied considerably depending on the contents of the colon and the proximity of the tip of the catheter to the main portal flow. The average reduction in the inferior mesenteric vein ammonia level produced by cooling was 463 mcg. per cent or 58 per cent of the original value. In the 14 dogs, there were only 4 in which the drop was less than 50 per cent. The lowest reduction was 25 per cent of the original value. Upon rewarming, the ammonia levels in the inferior mesenteric vein rose rapidly to precooling levels or higher. As evidenced in Table II, the arterial and peripheral venous levels rose in most instances during cooling. In the 9 dogs in which arterial ammonia level was

Table I. *Effect of temperature change on ammonia production of fecal cultures*

Fecal culture	*Incubation temperature (C.)*	*No. of determinations*	*Average mcg. % ammonia produced*	*% decrease in ammonia production*	*Average % decrease*
I	37.5°	8	174		
	30.0°	8	94	46	—
II	37.5°	10	787		
	30.0°	10	282	64	66
III	37.5°	10	1,440		
	30.0°	10	160	88	—

Table II. *Effect of general hypothermia to 30° C. on blood ammonia*

	Inferior mesenteric vein ammonia level (mcg. %)		*Femoral artery ammonia level (mcg. %)*		*Femoral venous ammonia level (mcg. %)*	
	37.5° C.	*30.0° C.*	*37.5° C.*	*30.0° C.*	*37.5° C.*	*30.0° C.*
	1,320	515	—	—	—	—
	250	150	—	—	—	—
	1,348	323	—	—	—	—
	560	122	—	—	—	—
	862	238	—	—	—	—
	656	214	52	111	—	—
	803	186	37	67	—	—
	629	246	69	76	—	—
	715	261	63	119	38	79
	564	156	60	107	38	153
	763	437	61	153	38	114
	610	359	76	61	61	91
	482	289	133	52	111	97
	1,583	1,172	53	61	61	80
Average % increase in blood ammonia level		0		77 (7 dogs)		75 (5 dogs)
Average % decrease in blood ammonia level		51.8 (14 dogs)		46 (2 dogs)		12 (1 dog)

Table III. *Effect of 3-hour anesthesia on blood ammonia level without hypothermia*

	Inferior mesenteric vein ammonia level (mcg. %)		*Femoral artery ammonia level (mcg. %)*		*Femoral venous ammonia level (mcg. %)*	
	Initial	*Final*	*Initial*	*Final*	*Initial*	*Final*
	552	522	90	79	61	54
	910	880	84	69	61	53
	354	369	69	77	40	47
	225	376	38	61	46	61
	378	401	45	60	61	69
Average % increase in blood ammonia level		29 (2 dogs)		40 (2 dogs)		16 (2 dogs)
Average % decrease in blood ammonia level		4 (3 dogs)		14 (3 dogs)		11 (3 dogs)

measured, it rose in 7 animals and was reduced in 2. In the 6 dogs in which peripheral venous ammonia level was measured, it rose in 5 and was reduced in 1. However, this rise in ammonia level in the peripheral circulation, when compared with the controls (Table III), failed to be statistically significant at 0.05 level with "F" tables. This may be the result of the small number of animals in these groups.

The 5 dogs under hypothermia, in which the pH and carbon dioxide tension were measured, showed varying degrees of acidosis. As noted in Table IV, the carbon dioxide tension was reduced slightly in all 5 animals. There did not appear to be any definite correlation with the degree of elevation of the peripheral ammonia levels and the degree of acidosis, other than the general observation that a reduction in pH was associated with an elevation in the ammonia content of arterial and femoral venous blood in most of the dogs.

DISCUSSION

Protein decomposition by enzymatic action of ammonia-forming organisms in the bowel is believed to be the main source of the

ammonia found in the blood. The action of these enzymes, largely urease and amino acid oxidase, is temperature-dependent as are all chemical reactions. It is of interest that Poland[10] found the temperature coefficient for plant urease to be 1.49 for the temperature interval of 30° to 40° C. Although the effect of temperature upon the growth rate of bacteria was not measured in this experiment, with the data established by Barber[1] in 1908 on *Escherichia coli,* the temperature coefficient for total rate of cell formation for the temperature interval 30° to 37° C. is approximately 1.7.

It is acknowledged that the reduction in ammonia formation afforded by incubation of fecal cultures at lower temperatures is dependent on many variables, such as the amount of substrate in the stool and the number and type of viable organisms. However, we believe hypothermia will reduce the ammonia formation significantly in each instance as demonstrated in this experiment with random fecal specimens without regard to these variables.

Lawrence and associates,[7] in their study on the effect of varying pH on total ammonia levels, found a small but consistent increase in plasma ammonia level with a decrease in pH. The converse occurred with an elevation of pH. The means employed to produce these changes in pH seemed to have little bearing on these changes in total ammonia.[7] These investigators found this elevation in ammonia level in the portal as well as arterial and peripheral venous blood. It is unlikely, therefore, in our study that the changes in blood ammonia levels under hypothermia are due entirely to pH changes; for with cooling to 30° C. the arterial and peripheral venous levels rose in most instances as expected with a decrease in pH, but the inferior mesenteric vein ammonia level was consistently reduced. It was noted, however, during the course of the experiment that the ammonia level in the inferior mesenteric vein tended to rise slightly during shivering and varied with the respiratory rate. An unexpected finding was a consistent rise in the ammonia content of the inferior mesenteric vein when mechanical ventilation with positive-pressure breathing was used. The mechanism for the latter phenomenon is not clear.

The tendency toward elevation of the peripheral venous and arterial ammonia levels may be due to the interplay of many factors; influence of blood-tissue pH gradient, decreased utilization by the liver, increased production by the kidney, or increased shunting around the liver. Regardless, these elevations in the peripheral ammonia levels should be viewed in light of the fact that the "free ammonia" expressed as pNH_3 or partial pressure of ammonia will be reduced in the animals cooled to 30° C. because of

Table IV. *Effect of hypothermia (30° C.) on ammonia, carbon dioxide tension, and pH*

Ammonia (mcg. %)		*pCO_2 (mm. Hg)*		*pH*	
37.5° C.	*30° C.*	*37.5° C.*	*30° C.*	*37.5° C.*	*30° C.*
Inferior mesenteric vein					
763	437	60.2	77.6	7.31	7.01
610	359	60.2	54.4	7.49	7.30
482	289	64.3	54.5	7.30	7.24
1,583	1,172	59.7	54.5	7.43	7.42
564	156	65.1	56.4	7.31	7.05
Femoral artery					
61	153	56.2	72.2	7.41	6.99
76	61	58.0	51.7	7.56	7.36
133	52	56.6	51.3	7.38	7.26
53	61	54.3	49.2	7.52	7.49
60	107	55.8	50.1	7.35	7.21

the reduction in pH and temperature. The ratio between nonionized or free ammonia and the ionized form of ammonia is fixed by the pH and pK of the plasma as expressed by the Henderson-Hasselbach equation.[6] It has been reported that the correlation between the "free ammonia" and symptoms of ammonia intoxication is closer than with the total ammonia concentration and that the free ammonia as expressed by pNH_3 is the more toxic and significant form of ammonia.[6]

Many of the data reported on the effect of hypothermia on the liver are relative to the protective influence of the reduced metabolic needs of the cooled liver in regard to hypoxia.[2] Whether this reduced metabolism of the liver of the cirrhotic patient under hypothermia would also interfere with the detoxification of ammonia to the extent that it would offset any reduction afforded in the formation of ammonia is a problem which needs study. However, the increasing number of reports[4, 11] suggesting the use of hypothermia as an adjunct at the time of portacaval shunt operation tend to sustain experimental evidence that hypothermia of moderate duration (12 hours) has no detrimental effect on liver function.[5] The results of our study suggest that hypothermia may be of benefit to the patient with ammonia intoxication in 2 ways, first by reducing the partial pressure of ammonia with consequent amelioration of symptoms and second by the reduction of the actual formation of ammonia within the bowel.

SUMMARY

1. Hypothermia will decrease the production of ammonia. Fecal samples incubated at 30° C. showed a marked decrease in ammonia formation when compared with similar samples incubated at 37.5° C.

2. The inferior mesenteric vein blood ammonia level in dogs cooled to 30° C. was consistently reduced. The average reduction in 14 dogs was 58 per cent of the original value. The peripheral venous and arterial blood ammonia levels rose in most dogs subjected to hypothermia. This rise, however, was not significant.

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Cancer cells in the blood in simulated colon cancer, resectable and unresectable: effect of fibrinolysin and heparin on growth potential

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Cancer cells are found in the circulating blood of many patients with primary resectable neoplasms.[5] This fact has resulted in renewed interest in the mechanisms whereby tumors spread and in the significance of the circulating cancer cells. The demonstration of cancer cells in the venous drainage of human colon cancers has led to the suggestions that early ligation of the vascular pedicle is essential and that chemotherapeutic agents be used at the time of operation.[3, 4] It seems important that methods be developed whereby controlled experiments may determine the effectiveness of different agents in controlling metastases via the bloodstream. Also requiring investigation are the conditions which may affect the viability and ability of the circulating cancer cells to produce metastases. Fibrin formation and clumping of cells might be expected to affect fixation of the cancer cells.

Pulmonary metastases of the VX_2 carcinoma of the rabbit were reported to be decreased by large amounts of heparin.[9] The thromboplastic nature of the VX_2 carcinoma was first thought to explain this phenomenon. It seemed wise to extend the studies of the influence of clotting factors to other tumors and to other materials which affect the clotting mechanism. Human fibrinolysin was found to be effective in greatly diminishing and preventing pulmonary metastases after intravenous inoculation of the VX_2 carcinoma, and of hepatic metastases after inoculation of the Brown-Pearce tumor in rabbits.[2] With the Walker 256 carcinosarcoma, a similar result was obtained when human fibrinolysin was given to rats prior to intravenous inoculation. In the control group there were 81 per cent pulmonary metastases, while in the treated group there were only 25 per cent pulmonary metastases. Other studies of the fate and survival of intravenously inoculated Walker 256 carcinosarcoma cells have been reported and are being studied.[7, 8]

The introduction of large numbers of cancer cells in 1 injection is of value in studying the methods of metastasis, but is certainly unlike any clinical situation. It was believed that a method should be used which is more in keeping with the usual clinical situation in which a tumor is explored and perhaps resected. This would be more likely to yield results applicable to cases in human beings. Such a method of producing a transplanted colon cancer in the rat has permitted the study of the spread of cancer by both lymphatic and vascular routes.[1] It provides a tumor that is satisfactory for the evaluation of hemodynamic and coagulation factors in the spread of cancer. The first purpose of this study was to correlate the presence of tumor cells in the blood with resectability of

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a simulated colon cancer in the rat, and to determine whether or not manipulation of the tumor altered the pattern of spread of the tumor cells. The second purpose was to determine whether alterations in blood coagulability would affect the vascular spread of tumor emboli when this type of tumor transplant was used.

MATERIALS AND METHODS

Materials. Two hundred forty adult female rats from the Charles River Farm of 150 to 200 grams each were used. The Walker 256 carcinosarcoma, which has been carried in solid form and in the peritoneum of rats in our laboratory for over 3 years, was employed. Heparin* (aqueous), 50 USP units, was injected intravenously and human fibrinolysin† (Cohn, fraction III-3), activated with streptokinase, 6,000 units per kilogram of body weight, was given intravenously prior to manipulation of the tumor.

Method. The simulated colon cancer was produced in the rats by a previously reported technique.[1] A piece of solid Walker 256 carcinosarcoma in a gelatin capsule was inverted into the cecal wall at the cecal appendical junction.

Two weeks after the implantation, all animals were re-explored and were divided into 1 group with resectable and another group with unresectable tumor, according to the size and degree of spread of the tumor. If the tumor was localized to the cecal pouch and was less than 1.5 cm. in diameter and there were no grossly palpable lymph node metastases or other gross evidence of spread, it was considered resectable. If the tumor was 1.6 cm. or more in size or lymph node metastases, ascites, or peritoneal implants were present, it was considered unresectable.

At the time of re-exploration blood samples were drawn from the portal vein, vena cava, femoral vein, jugular vein, and aorta (not all in the same animal), and the blood studied for tumor cells (Seal's[10] technique). Blood from these sites was also inoculated into weanling rats to determine the viability and the transmissibility of cancer cells in the blood. Twenty-five recipient (weanling) animals were used for each donor animal.

In both, animals with resectable and those with unresectable tumor, the effect of a 1-minute digital massage of the cecal tumor on the number and transmissibility of cancer cells in the blood was studied. In approximately half of the animals in the group of rats with tumor considered resectable, the cecal tumor was removed after massage. In alternate animals of each group, saline solution, heparin, or human fibrinolysin was infused either before or after massage.

The recipient (weanling) rats which had received the subcutaneous injection of blood were observed for 9 weeks. If there was no obvious growth of tumor at 9 weeks, they were subjected to massage of the implantation site and laparotomy at 9, 11, 13, and 15 weeks, and were then observed to a total of 18 weeks after the injection of the blood. They were then sacrificed, and a careful postmortem examination was made.

RESULTS

All the animals (100 per cent) with tumor implanted in the cecal pouch developed a neoplasm in the bowel wall. Of the animals explored at 2 weeks after implantation, 38 per cent were considered to have resectable tumor, and 62 per cent had unresectable tumor by the established criteria.

Histologic study of a branch of the mesenteric vein in several rats with unresectable tumor showed tumor emboli in the lumen.

Group with resectable tumor (38 per cent). Samples of blood were taken from the portal vein, vena cava, and aorta. No free cells were found in any of these vessels in the control group. When the cecal tumor was massaged for 1 minute, tumor cells were found in the blood samples of all the control animals with resectable tumor. After resection of the tumor, the cells disappeared in most cases (Fig. 1). When blood from the vena cava was injected into the recipient (weanling) rats at the time of massage, 1 of

*Liquaemin, Organon Inc., West Orange, N. J.
†Thrombolysin, Merck Sharp & Dohme, West Point, Pa.

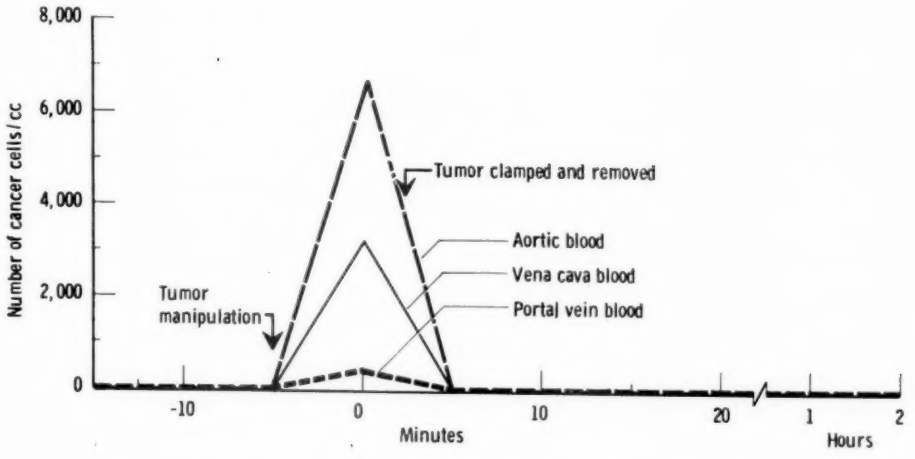

Fig. 1. A study of aortic, portal, and vena caval blood of animals with resectable tumor. Note shower of cancer cells at time of massage of tumor. Cancer cells disappeared from circulating blood after 5 minutes even if tumor was not removed.

25 rats (4 per cent) showed growth at 9 weeks (Table I). When the 24 remaining recipient rats were subjected to repeated laparotomies and massage of the subcutaneous implant sites, 6 or 25 per cent developed tumor at the implant site by 18 weeks.

With aortic blood from rats with resectable tumor, subcutaneous inoculation resulted in tumor growth in 2 or 8 per cent of the 25 rats at 9 weeks. When the remaining 23 recipient rats were subjected to laparotomies and massage of the tumor, 8 or 35 per cent had subcutaneous tumor growth by 18 weeks (Table II).

Group with unresectable tumor (62 per cent). Study of the rats in the group considered to have unresectable tumor showed a different picture. All animals showed tumor cells in blood from the portal vein, vena cava, and aorta. Under control (preoperative) conditions, there were approximately 42 cells per milliliter in the blood from the portal vein. With manipulation of the tumor, there was a temporary increase to an average of 296 cells per milliliter followed by a return to the preoperative level. Many more tumor cells were noted in blood from the vena cava and the aorta (Fig. 2) than in blood from the portal vein. Cells were not only present under control circumstances, but also increased markedly in number with massage of the tumor. It should be noted that in these rats with unresectable tumor, no cells were found from the jugular vein or the femoral vein prior to manipulation. However, after massage of the tumor in rats from group with unresectable tumor, large numbers of cells were found in blood from the jugular and femoral veins (approximately 3,000 cells per milliliter).

In all cases, whether the tumor was resectable or unresectable, increase of cells in the blood was marked after manipulation.

When the blood from the vena cava or aorta of animals with unresectable tumor at time of massage was injected into donor (weanling) rats, tumor growth occurred in 100 per cent of the animals at 9 weeks (Table II). This was in contrast to the very low rate of tumor growth at 9 weeks in the animals with resectable tumor.

The effect of heparin and fibrinolysin in animals with resectable tumor. It has already been noted that control animals with resectable tumor showed no free cells in the blood prior to manipulation. Significant numbers of cells appeared (up to 6,000 per milliliter) after manipulation, but there was a rapid decrease to no cells after resection (Fig. 1). It also was shown that even with tumor cells in the blood at the time of tumor massage, only 1 or 2 out of 25 recipient rats would develop tumors subcutaneously. With repeated massage, tumor growth was found in 25 to 35 per cent (of the recipient) at 18 weeks after injection of the blood taken from

Table I. *Vena cava blood injected subcutaneously in groups of 25 rats*

Resectable	
No. of rats injected subcutaneously with approximately 6,000 t.c. (1 minute after manipulation)	25
No. of takes	1
Per cent takes	4
Repeated laparotomies and manipulation of site of implant	24
No. of takes	6
Per cent takes	25
Unresectable	
No. of rats injected subcutaneously with approximately 19,000 t.c. (1 minute after manipulation)	25
No. of takes	25
Per cent takes	100

Table II. *Aortic blood injected subcutaneously in groups of 25 rats*

Resectable	
No. of rats injected subcutaneously with approximately 6,000 t.c. (1 minute after manipulation)	25
No. of takes	2
Per cent takes	8
Repeated laparotomies and manipulation of site of implant	23
No. of takes	8
Per cent takes	35
Unresectable	
No. of rats injected subcutaneously with approximately 14,000 t.c. (1 minute after manipulation)	25
No. of takes	25
Per cent takes	100

Table III. *Vena caval blood (1 ml.) injected subcutaneously in groups of 25 rats*

	No. of rats	*No. of takes*	%
Control	25	25	100
Fibrinolysin (6,000 U./Kg.)	25	5	20
Heparin (50 USP units)	25	4	16

the animals with resectable tumor at the time of manipulation (Tables I and II).

When 50 USP units of heparin was injected intravenously just prior to manipulation of the primary tumor, fewer cells were found in the blood after manipulation than in the control group (Fig. 3). However, cells could be found in the circulation for 2 hours, in contrast to their presence for only 5 minutes in the controls.

A similar result was noted with infusion of fibrinolysin prior to manipulation (Fig. 3).

Group with unresectable tumor treated with heparin and fibrinolysin. In the control animals with unresectable tumor, many tumor cells were present in blood from the vena cava and the aorta, and after manipulation there was a significant rise to high levels in blood from the vena cava and aorta (Fig. 4). When heparin was injected intravenously before manipulation, the number of cells in the vena caval blood decreased. At the time of manipulation there was only a slight rise (Fig. 4) instead of the marked rise seen in the controls (Fig. 2). After this slight rise, the decline in number of cells continued and the effect lasted for at least 2 hours. Blood from these same animals with unresectable tumor injected with heparin prior to manipulation produced subcutaneous tumors in only 4 of the 25 donor animals (16 per cent) compared with the 25 or 100 per cent takes in the controls (Table III).

When human fibrinolysin (6,000 U. per kilogram) was injected intravenously 5 minutes before manipulation of the tumor and blood from the vena cava was studied, it was found that the number of cancer cells fell to low levels and remained there for 2 hours despite the manipulation. There was a minimal rise in the number of circulating cancer cells at the time of manipulation (Fig. 4). Furthermore, subcutaneous injection of vena caval blood resulted in tumor growth at 9 weeks in only 5 or 20 per cent of the 25 donor animals (Table III).

When human fibrinolysin was injected intravenously after tumor manipulation, the number of cells in the portal vein blood decreased to a level below that seen prior to manipulation. In these same animals the cancer cells disappeared from the aortic blood for at least 4 hours. In animals not injected with fibrinolysin, the number of cells in the blood from the aorta returned to the premanipulation level after the peak which followed manipulation of the tumor. Unfor-

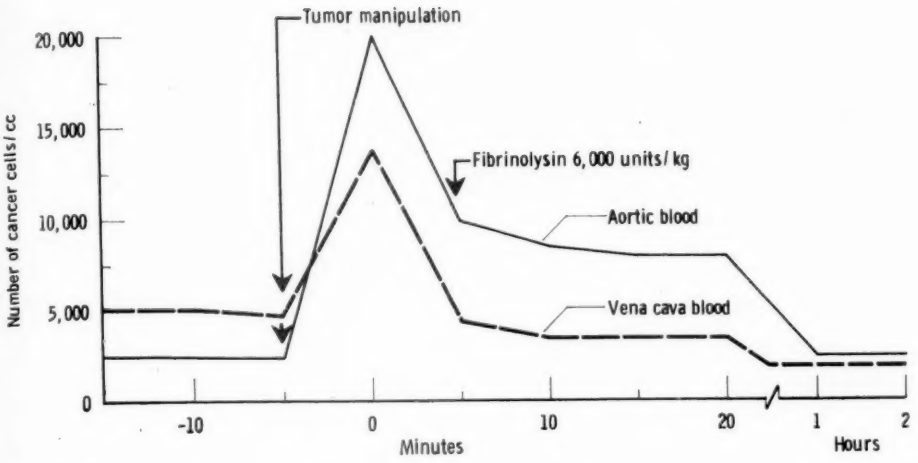

Fig. 2. Study of aortic and vena caval blood of animals with unresectable tumor. Note presence of cancer cells before manipulation of the tumor, rapid increase at time of massage, and then fall to the original control level in one-half hour. Note different scales of Figs. 1 and 2.

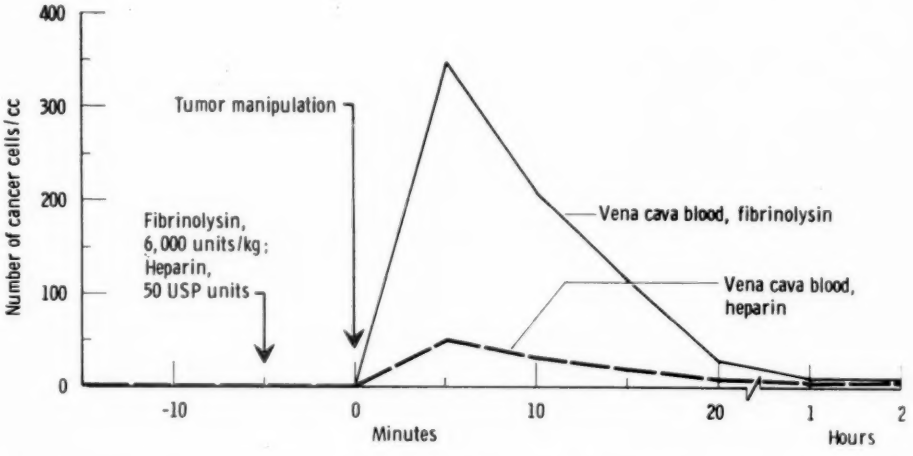

Fig. 3. Study of vena caval blood of animals with resectable tumor treated with heparin and fibrinolysin prior to manipulation of the tumor. Note the decrease in number of cells found immediately, but their prolonged presence.

tunately there are no data concerning the growth in donor animals under these circumstances, but it should be noted that in no instance has there been growth in any recipient animal without obvious tumor cells in the blood.

DISCUSSION

It is probably significant that in this series of animals the rats with resectable tumor did not have detectable tumor cells in the blood, while all of the animals with unresectable tumor had a large number of circulating tumor cells in blood from the portal vein, vena cava, and aorta. Also significant is the finding that after massage of the resectable tumor, a number of tumor cells were found in the blood of the portal vein, vena cava, and aorta. The tumor cells remained in the circulation for 5 minutes whether or not the tumor was removed (Fig. 3). This demonstrates the very rapid removal of the tumor cells from the circulation in animals with small resectable tumors. The method of removal is of sufficient importance to warrant active investigation.

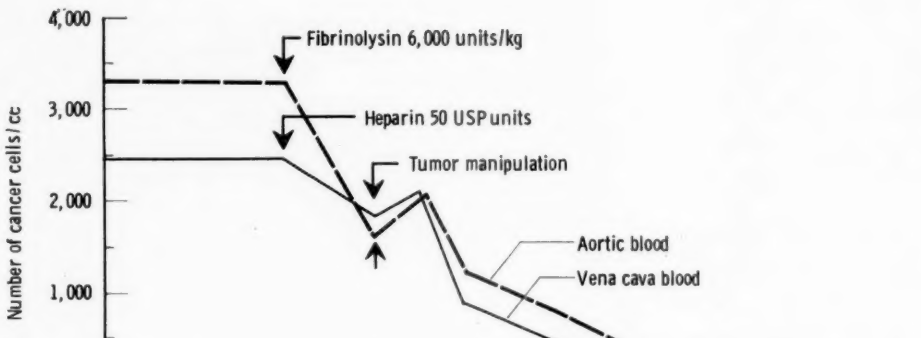

Fig. 4. A study of vena caval and aortic blood of animals with unresectable tumor. Note effect of heparin and fibrinolysin in lowering control cell count and decreasing markedly the rise after manipulation. The number of cancer cells continues to fall to almost zero within 30 minutes.

After manipulation of the unresectable tumors, there was a marked increase in the number of cells, but the intriguing finding was that the greatest number of cells were found in blood from the vena cava and aorta, but not in that from the portal vein. This might be attributable to spillage of tumor cells into the systemic circulation, but when one considers that this observation was made also in the animals with tumors considered resectable, this does not seem likely. It seems more logical to suspect that once the tumor cells pass through the liver, they remain in the systemic circulation for a much longer period of time. This finding is similar to an observation we made with infused tumor cells.[8] When the cells were injected into the femoral or the jugular vein, large numbers of cells were found in the vena cava and aorta, but none in the portal vein.

It is possible that in the present case cells which are spilled into the portal system pass through the liver and then continue to circulate. A large number are flowing through the aorta at all times, but are probably filtered out in the splanchnic bed. Another possibility is that massage increases the number of cells in the systemic circulation by opening portal systemic shunts with abnormally high portal pressures through the liver or elsewhere.

The effect of heparin and fibrinolysin on the circulating cancer cells is difficult to explain. With both agents, the number of cells present in animals with unresectable tumor is decreased and the rise after manipulation is minimal. They also decrease the number of tumor cells found in the blood after manipulation of the resectable tumors. In the treated group with resectable tumor, however, the cells continue to circulate for a longer period of time.

The results of the growth of tumor in the recipient animals are particularly interesting. The presence of dormant tumor cells is indicated by the increased take from 8 to 25 or 35 per cent when the tumor site was massaged and repeated laparotomies were performed. This is similar to the observations of Fisher and Fisher with hepatic metastases.[6]

The effect of heparin and fibrinolysin on animals in the group with tumor considered unresectable is very significant. Under control circumstances, blood from those animals produced 100 per cent takes in the recipients. When heparin or fibrinolysin was infused just prior to massage of the tumor, only 16 to 20 per cent of the recipient rats developed tumors at 9 weeks. These findings confirm the results of studies carried out with tumor cells injected intravenously, thus indicating that fibrinolytic enzymes or heparin have an effect on the number of circulating cells and the viability or transmissibility of the cancer

cells circulating in the blood. The reason for this decrease in the number of cells in the circulation and the decrease in transplantability of cells present in the circulation is still a subject for speculation. It might be necessary for the cells to group or clump and to be fixed by some kind of fibrin film before they can begin to grow either in the capillaries of the lung or other organs or in the subcutaneous tissues of the recipient rats. Heparin or fibrinolysin could prevent this fibrin from accumulating. It is possible that heparin and fibrinolysin affect the tumor cells themselves, but in previous studies, fibrinolysin in vitro failed to alter the transmissibility of the Walker 256 carcinosarcoma.[7] The same has been shown to be true of heparin (unpublished data). It is also conceivable that fibrin coating of the cancer cells protects them from destructive elements in the animal's blood.

These two agents have only one thing in common—they alter the clotting mechanism. And they accomplish even this by different means. Heparin prevents clotting by altering the thrombin-fibrinogen reaction to produce fibrin, and fibrinolysin alters clotting by digesting fibrinogen or lysing the clot after it is formed.

Additional investigations of the effect of fibrin formation or clotting on metastases and growth of malignant tumors are obviously needed. These should include studies of the effects of other anticoagulants on the growth and metastasis of tumor. The effect of alterations of the mechanism by fibrin formation or clotting must also be investigated.

CONCLUSIONS

In rats with small tumors considered resectable and without evidence of local extension or distant spread, no cancer cells were found in the blood. At the time of manipulation of the local tumor, cells were found in the blood stream, but they disappeared within 5 minutes. These tumor cells were transmissible subcutaneously in a small percentage of recipient animals. Manipulation of the donor sites increased the rate of growth. In rats bearing tumors considered unresectable, cancer cells were found in the circulating blood under control circumstances, and there was a sharp rise in the number of tumor cells at the time of manipulation and for a few minutes thereafter. There was 100 per cent take of tumors in the recipient animals under control circumstances. Injection of human fibrinolysin or heparin resulted in a marked diminution in the number of tumor cells in the blood of animals with unresectable tumors and a decrease in the number of cells at the time of manipulation in animals with both resectable and unresectable tumors. There was a marked decrease in the number of tumor growths in recipient animals.

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A venous cannula for use in experimental animals

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It is difficult to obtain multiple samples of portal blood or of blood from other inaccessible deep veins in the course of investigations in the ambulatory experimental animal. Expensive guides machined from stainless steel have been described which accomplish this purpose to some degree. These devices utilize the principle of directing the needle to the entrapped vein. Although the steel devices usually function satisfactorily, they have definite limitations. A more simple and inexpensive device with greater flexibility should be available.

Teflon* in the solid form can easily be made into a slightly flexible, nonreactive cannula without special machinery. Teflon rod, used in industry in the manufacture of bearings, was found to be ideal for the fabrication. The physical characteristics of this material[2] make it ideal for permanent implantation in living tissues. It is slippery to touch, completely nonwetting, and nonreactive. It may be shaped without difficulty with a scalpel blade for any minor changes in contour. The material is readily available from plastic dealers as rod stock in any diameter and in any length.

In the cannula construction, an open funneled end is made to receive the aspirating needle (Fig. 1, *A*). A tunnel is formed at the opposite end which may be opened and then closed over the vein to be aspirated (Fig. 1, *B*). The tunnel is formed first from the rough rod before shaping is started. A hole the size of the vein to be aspirated is drilled perpendicularly through the rod. The distance of the hole from the funnel end of the cannula is determined by the average depth of the vein beneath the skin of the animal. The rod is then cut off distal to the hole and shaped by hand trimming to remove the rough corners around the vein tunnel. Access is made to the tunnel by cutting along the lateral aspect (Fig. 1, *C*) and placing 2 small holes (Fig. 1, *D*) for reapproximation of the tunnel around the vein. Two small sutures are used for this closure, and the flexibility of the plastic allows for an indefinite number of openings and closings without damage to the cannula.

The shaft of the cannula is then shaped to the contour shown in Fig. 1. This allows fixation of the cannula in the fascia beneath the skin of the animal. The funnel end remains the same size as the diameter of the original rod stock. The taper of the inside of the funnel is long enough so that insertion of a needle is easy. The needle tunnel (Fig. 1, *E*) at the apex of the funnel is drilled to fit an 18 gauge needle.

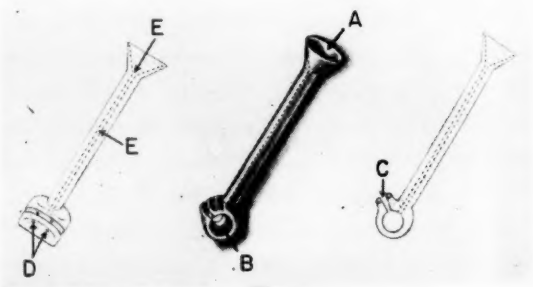

Fig. 1

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*Polytetrafluoroethylene.

This cannula may be made in various sizes. It can be left in the animal for an indefinite period without local reaction. There is a low incidence of thrombosis of the vessel under study if small, sharp needles are used and if care is exercised in the aspiration of the sample. Samples have been drawn from the same vein as often as every 15 minutes without thrombosis.

SUMMARY

A Teflon vessel cannula has been described. The use of solid rod Teflon allows the fabrication of a device which is effective, inexpensive, and easily adaptable to a wide variety of applications. The material is nonreactive in living tissues. The relative softness of this plastic makes it ideal for fabrication without special tools and minor variations can readily be made at any time. The cannula can be boiled or steam autoclaved or soaked in sterilizing solutions without deterioration.

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The use of fascial grafts in experimental bladder wall defects: preliminary report on application in the repair of exstrophy of the bladder

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Exstrophy of the bladder can be repaired by means of various surgical procedures. A large number of procedures, both experimental and clinical, have been described in the literature, but none is entirely satisfactory. At the moment it appears that primary repair of the bladder is the best. One of the problems encountered with this operation is that when the bladder is small, it has proved difficult and at times impossible to achieve a primary repair. One method of solving this problem would be to use a graft to enlarge and close the bladder.

We became interested in determining experimentally whether a "free fascial graft" would "take" in the presence of bladder mucosa and whether such grafts would interfere with normal bladder function and growth. When our experimental studies on dogs proved to be successful, the same surgical procedure was performed clinically and a fascial graft was used for the repair of exstrophy of the bladder in 2 children.

METHOD

Ten adult mongrel male and female dogs weighing from 18 to 25 pounds were selected for the experiments. There were no preoperative preparations. The first 2 experiments were performed on male dogs and because difficulty was encountered in urethral catheterization, female dogs were used for the other 8 experiments. Sterile technique was used for all procedures. Anterior rectus fascia, which is well developed and easily accessible, was the source of our grafts.

After anesthetization with intravenously administered Nembutal, a suprapubic longitudinal incision was made and the subcutaneous tissue dissected from the anterior rectus fascia. The anterior sheath of the rectus fascia was dissected from the anterior rectus muscle (Fig. 1). The size of the graft averaged 3.5 by 5 cm. The peritoneum was incised and bladder and ureters identified. In the first 2 experiments approximately 2 by 3 cm. of bladder wall was excised. The defect was repaired with a 2 by 2 cm. graft. In the remaining 8 experiments all of the bladder wall but 1 cm. above each ureteral orifice was excised (Fig. 2). The bleeders were clamped and ligated with No. 5-0 plain catgut. The fascial graft in this series averaged 3 by 5 cm. This was approximated to the bladder mucosa with interrupted No. 5-0 plain catgut sutures. The muscular layer was approximated to the fascia with inter-

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rupted No. 5-0 chromic catgut (Fig. 3). The bladder was filled with sterile saline and examined for leakage. The bladder area was not drained and the urethral catheter was removed at the end of the procedure. The edges of the defect of rectus fascia were approximated with No. 5-0 interrupted silk sutures. The dogs were placed in special cages which permitted the accurate collection of urine. The urine volumes were charted daily for the first 5 days. The dogs were checked for residual urine at monthly intervals. Intravenous pyelograms and cystograms were performed at the end of the first, third, and sixth months after operation. Blood urea nitrogen, sodium, potassium, chloride, and carbon dioxide levels were determined prior to operation and at the third postoperative month. Urine cultures and colony counts were performed prior to operation and at monthly intervals postoperatively. Histologic sections of bladder wall and fascial grafts were taken at various intervals postoperatively.

Fig. 1. Anterior layer of rectus sheath dissected from rectus muscle of dog No. 506.

RESULTS

There were no postoperative deaths or fistula formations in the 10 experiments. During the first 3 postoperative days, the dogs voided frequently. The amount of urine voided each time gradually increased during the first 2 weeks. Residual urine measurements were obtained immediately after the animals voided and the volume never exceeded 5 ml.

One month after operation urine cultures were negative in 8 animals and in the remaining 2 there was a *Staphylococcus aureus* growth of one-half million per milliliter. The results of urine cultures were negative in all animals at the end of the third month.

After operation the blood urea nitrogen, as well as the serum sodium, potassium, chloride, and carbon dioxide levels remained unchanged from preoperative levels. In all experiments, the upper urinary tracts were radiographically normal. Cystograms performed 1 month after operation outlined a small urinary bladder with irregular contours at the site of the fascial graft. Sanguineous urine was observed after the insertion of a Foley catheter. After 2 months the bladders were enlarged and the contours were smooth. The urine was clear after catheterization. Three months after operation cystograms showed normal bladders (Fig. 4).

Bladder function was evaluated by measurement of residual urine and by artificial stimulation of the bladder. At operation prior to the excision of a large segment of bladder, we were able to simulate a sustained detrusor contraction by attaching electrodes bilaterally to the pelvic nerves and applying a 6 v. stimulus. The intraluminal bladder pressure was increased from 15 cm. H_2O to 45 cm. H_2O. The same procedure was repeated at a subsequent operation after the final gross examination of the bladder graft site. The increase in the intraluminal bladder pressure at this time was approximately the same as that recorded from the intact bladder prior to grafting.

By the end of the first month, the graft was less than half of its original size and

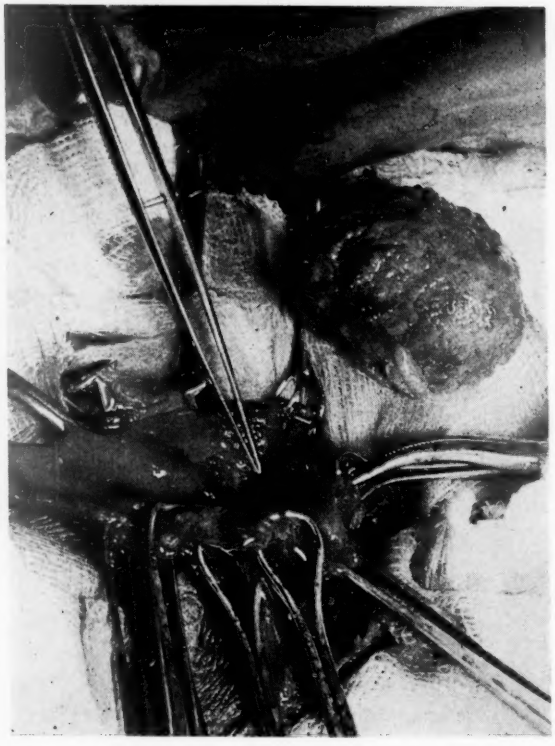

Fig. 2. Bladder remnant of dog with approximately 1 cm. of bladder wall above each ureteral orifice. Forceps points to left ureteral orifice. The excised portion of bladder is located in the upper part of photograph.

the bladder was normal in shape. Its internal surface was smooth except for the fascial graft, which was covered by healthy granulation tissue. By the end of the third month, the fascial graft was reduced to less than 1 cm. in width and 2 cm. in length. The external surface of the graft was smooth, glistening, and firm (Fig. 5). In all experiments the bladder mucosa covered the fascial graft completely (Fig. 6). An incision through the graft site showed it to be gritty, firm, and thickest at its most central portion (Fig. 7). After a period of 6 months, no calculi could be observed in any of the bladders.

Transitional epithelium covered the fascial remnant completely (Fig. 8). This remnant consisted of thick connective tissue. In 3 of the 10 experiments there were small foci of ectopic bone. This is a finding also reported by Baret and associates.[1] The bladder wall surrounding the graft appeared normal.

DISCUSSION AND CONCLUSIONS

In 1953 Baret and his colleagues[1] used a rectus fascia and muscle graft in the experimental repair of bladder wall defects in dogs. They reported a high incidence of fistula formation which was attributed to inadequate bladder drainage. We believe that the muscle and fascia graft combination may have contributed to the formation of fistulas. Suturing of the muscle makes it permeable. The muscle portion of the graft, without an intact vascular supply, must have undergone necrosis. The combination of necrotic tissue and urine leakage must have contributed significantly to fistula formation.

In the present study rectus fascia without muscle was used to repair the defect in the bladder wall. There was no fistula formation in any of the 10 dogs. Furthermore, all studies of renal and bladder function yielded normal results after operation. With the fascial grafts the blood chemistry studies showed no significant changes like those that occurred with absorbing mucosal grafts. All of the fascial remnant was eventually completely covered with normal bladder mucosa. The fascia did not inhibit the rapid regeneration of bladder mucosa.

At the end of 3 months, cystograms showed a bladder, normal in size and shape, without ureterovesical backflow. We believe that reflux was absent because the ureterovesical trigone was not disturbed and also because prolonged elevations of intravesical pressure and chronic bladder infection were lacking.

The fascial graft did not interfere with complete bladder emptying as demonstrated by the negligible amount of residual urine. The bladder remnant not only maintained its resiliency and adaptability to increasing bladder pressure, but also exhibited an efficient emptying detrusor mechanism. The integrity of the bladder muscle was further demonstrated by the fact that an adequate sustained contraction was obtained on stimulation of the pelvic nerves.

The gross anatomic and histologic studies confirmed the ability of the bladder remnant to enlarge its size by gradually adapting itself

to increasing volumes and pressures. The results of histologic studies left no doubt of the complete regeneration of the transitional epithelium. The microscopic bony spicule formation was probably due to the direct effect of bladder mucosa when it was in contact with the fascia. As soon as the entire surface of fascia was covered with the neouroepithelium, the ectopic bone formation was arrested. The ectopic bone did not interfere with bladder function.

A fascial graft is a worth-while adjunct in the primary repair of exstrophy of the bladder. In some patients the bladder remnant is so small that it cannot be turned into a viscus and in others it is so small that it can not accommodate a catheter for drainage. Moreover, in such cases attempted closure under tension will cause the bladder wound to break down and a fistula to develop. The problem is further aggravated by the postoperative mucosal edema. In our series of 29 patients with primary closure of the bladder, 6 had no urinary output for from 48 to 72 hours after the repair. One additional patient had no urinary output for the first 5 days after the operation and an elevation of serum potassium to 6.7 mEq. per liter. The formation of a small bladder by primary closure and superimposed postoperative mucosal edema may cause an elevation of the intraureteral pressure to levels above those compatible with proper functioning of the kidneys and the ureters. This favors the development of severe urinary infection. The additional problem of fistula formation may also originate during this period. The complications of this period may be avoided by the use of a fascial graft which will adequately enlarge the bladder reservoir.

Our experiments have demonstrated the easy accessibility and sufficient pliability of a fascial graft. The blood supply to the graft is not jeopardized with a fascial graft as it is with a seromuscular graft or loop of ileum or rectum.

Shoemaker and Marcucci[2] in 1956 had hoped that their seromuscular graft would

Fig. 3. The fascial graft, measuring 3.5 by 5 cm., sutured to the dog's bladder remnant.

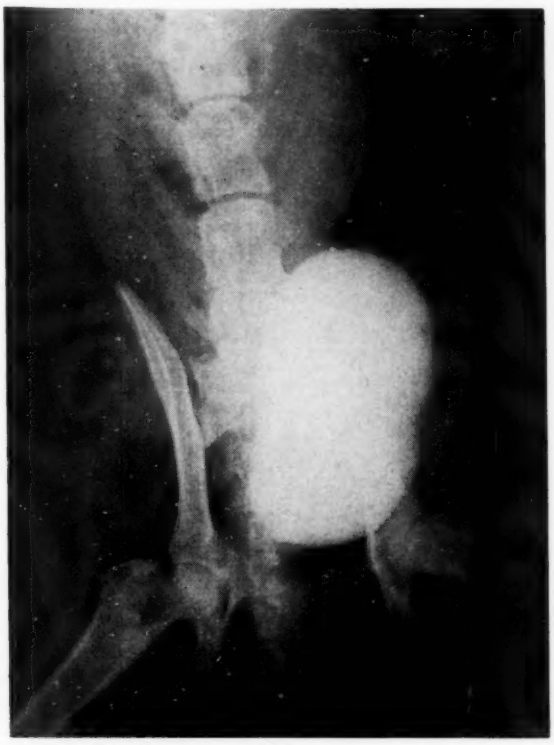

Fig. 4. A cystogram performed on the dog 3 months postoperatively outlines a bladder normal in size and shape.

Fig. 5. The external surface of dog's bladder, 3 months after operation, is smooth and soft. Fascial graft is reduced to less than one-third of its original size.

function as an integral unit of the bladder. We believe that this is impossible because the stimulus which acts upon the bladder muscle has no way of being transmitted to the seromuscular graft. This graft simply helps to form a part of the bladder wall. A seromuscular graft will interfere with sustained detrusor contraction because it has no way of contracting simultaneously with the bladder remnant. The graft will allow some loss of emptying power because it will expand with the increased intraluminal pressure and act as a bladder diverticulum. The fascial graft affords an adequate bladder reservoir initially. As the bladder wall enlarges and the mucosa regenerates, the graft shrinks proportionately. The fascia is not distensible and allows the entire bladder remnant to expand. It is the latter process which makes possible the gradual enlargement of the bladder remnant and shrinkage of the graft after it has fulfilled its usefulness.

Influenced by the results with experimental fascial grafts, we have employed rectus fascia autografts in 2 patients for primary closure of exstrophy of the bladder.

CASE REPORTS

Case 1. M. R. was a girl, 2 years and 10 months of age. The bladder remnant measured 3 by 3 cm. and the mucosa was friable and hypertrophied. Excretory urograms showed large dilated ureters bilaterally. Ureteral peristalsis was poor bilaterally. Urine culture and colony count showed that there were over 3 million *Aerobacter aerogenes* per milliliter. The child was treated with a specific antibiotic for 5 days and then underwent bilateral iliac osteotomies.

Three days later a primary closure of the bladder was performed. The redundant folds of mucosa were excised and the bladder mucosa was approximated with interrupted plain catgut sutures. An incision was made around the periphery of the bladder and cephalad the peritoneum was separated by blunt dissection. Laterally, the bladder wall was separated from the rectus muscle by sharp dissection. The bladder neck and urethra were freed sufficiently to allow the mucosal edges to be brought together without tension. The urethral mucosa was approximated with interrupted No. 5-0 plain catgut sutures. The approximation was carried out to about 1 cm. beyond the bladder neck. In the region of the bladder neck, the mucosal suture line was reinforced with flaps of fibrous tissue. No urethral splint was used.

A transverse incision was made in the left upper quadrant of the abdomen and a 2.5 by 2.5 cm. portion of anterior rectus fascia was excised. The fascial defect was repaired with interrupted No. 5-0 silk sutures. The skin incision was closed with a continuous No. 5-0 plain catgut subcuticular suture. The fascial graft was sutured to the bladder mucosa with interrupted No. 5-0 plain catgut sutures. The muscular layer was then sutured to the fascia with interrupted No. 4-0 chromic catgut sutures. A No. 12 Malecot catheter was inserted through an incision made in the dome of the bladder wall and fixed to it with a No. 5-0 chromic catgut suture. The pubic bones were approximated with 3 interrupted No. 2-0 chromic catgut sutures and the medial borders of the rectus muscles were sutured together with interrupted No. 4-0 chromic catgut sutures. The skin was approximated with interrupted No. 5-0 silk sutures.

Within 24 hours after operation, the urinary output was normal. The postoperative course was uneventful and the suprapubic catheter was removed on the fourteenth postoperative day. Six

Fig. 6. The internal surface of dog's bladder 3 months after operation indicates normal appearance of the bladder mucosa. To left of forceps is fascial graft covered with bladder mucosa.

Fig. 7. An incision through the fascial graft site of dog's bladder after 3 months demonstrates that grossly the graft is reduced in size and completely covered by bladder mucosa.

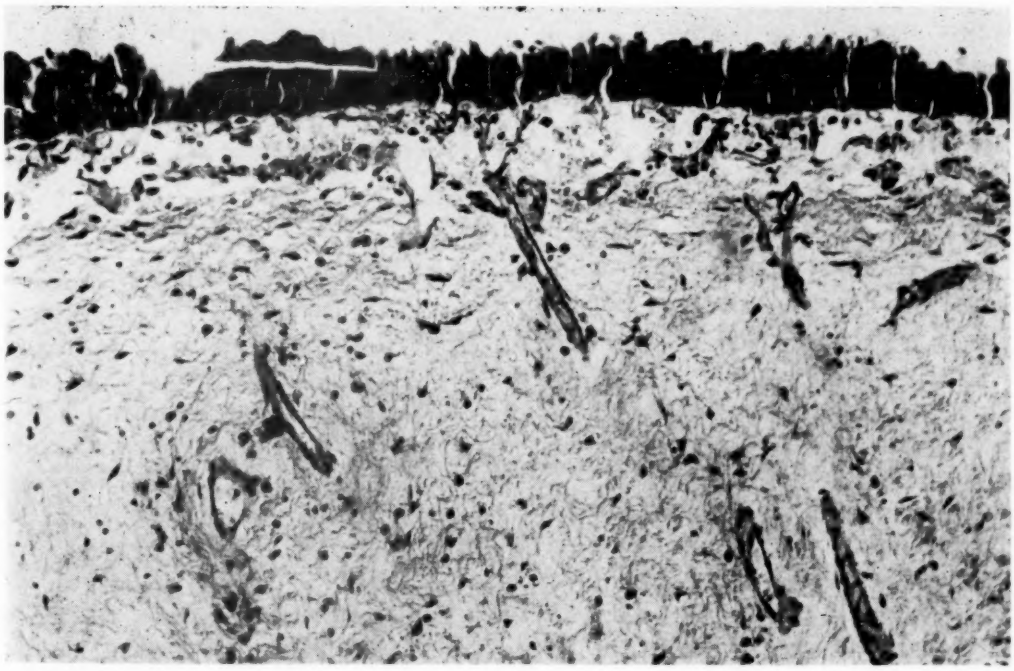

Fig. 8. A thin layer of transitional uroepithelium overlying the fascial remnant in a dog 3 months after operation.

months after the repair, the patient was admitted to the hospital and a cystogram was performed which showed a bladder normal in shape. The bladder capacity was 45 ml.

Case 2. L. R. was a 5-day-old white boy who was admitted to the hospital because of bladder exstrophy. The bladder remnant measured approximately 2.5 by 2.5 cm. The urine contained over 2 million *E. coli* per milliliter. Ureteral peristalsis was normal in the right ureter and irregular and infrequent in the left ureter. The intravenous pyelogram outlined a dilated upper urinary tract bilaterally. The urinary tract infection was treated with a specific antibiotic for 6 days. Bilateral iliac osteotomies were performed and 3 days later the primary closure of the bladder remnant was carried out. The bladder remnant was small and the same procedure as described in Case 1 was performed, except that the corpora cavernosa were freed up to their attachments to the pubic bones. The corpora were approximated with interrupted No. 4-0 chromic catgut sutures over the newly formed urethra. The urinary output was satisfactory within 24 hours. Three weeks after the bladder repair, the suprapubic catheter was removed and the patient was discharged. Seven months later he was admitted to the hospital for the repair of bilateral inguinal hernias. During this admission the urine contained 3 million *Aerobacter aerogenes* per milliliter and specific antibiotic therapy was continued for 6 days. A cystogram outlined an oval-shaped bladder with a capacity of 30 ml. The patient has had a negative colony count since his last admission.

The use of the fascial grafts in the 2 patients confirms their usefulness in primary closure of bladder exstrophy. Without a graft of this nature, we would have had to perform a procedure for urine diversion in the 2 patients. We believe that the use of a fascial graft allowed for an enlarged bladder reservoir which did not interfere with the urine flow to the bladder.

SUMMARY

Rectus fascia autografts were used successfully to repair experimental bladder wall defects in 10 dogs. Repeated gross and histologic studies of the reconstructed bladder demonstrated the remnant to be expanding and growing concomitantly with regression of the fascial graft.

Normal bladder function and capacity were obtained. Biochemical studies of the blood as well as intravenous pyelograms showed normal renal function.

Postoperative wound complications were not encountered.

The practical application of the fascial graft in 2 children with exstrophy of the bladder is described. The preliminary early results are satisfactory and encouraging. However, sufficient time has not elapsed for evaluation of the late results of the fascial graft with respect to the development of the bladder and renal function.

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Vesicoileosigmoidostomy in the treatment of exstrophy of the bladder

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In a previous publication from the Los Angeles Childrens Hospital,[3] the use of different intestinal segments to enlarge the exstrophied bladder was described. The utilization of isolated loops of ileum and sigmoid colon as urinary conduits distal to the reconstructed bladder was studied in 11 patients.* The combined use of both of these intestinal elements as a conduit, that is, vesicoileosigmoidostomy (Fig. 1), has been discussed in a previous report.[5]

Six children with exstrophy in whom previous reconstructive procedures had proved unsuccessful have been operated upon by this procedure with a uniform technique.

HISTORIES OF 6 PATIENTS WHO UNDERWENT VESICOILEOSIGMOIDOSTOMY FOR EXSTROPHY

Five of the children were girls and 1 was a boy. The average age at the time of this procedure was 5 years (range 16 months to 7 years, 6 months).

In 3 patients, exstrophy was associated with additional major upper urinary tract disease. Renal agenesis (left) had been suspected in the patient in Case 1 from the date of the initial excretory studies and was confirmed at laparotomy. Ureterectasis without structural ureterovesical obstruction had been observed in the patient in Case 2 prior to the initial operative procedures. It may represent neurogenic megaloureter. Unilateral ureterectasis without obstruction developed in the patient in Case 6 during the course of the series of plastic procedures performed (Table I).

Imperforate anus, noted in Case 1, was of the membranous type (Ladd type II), apparently readily corrected on the second day of life. Other congenital defects included an infantile rectal prolapse (Case 5) which was sufficiently severe to prompt operative correction when the patient was 6 months old. The absence of digits was noted in 1 patient.

All patients had undergone at least 1 previous surgical procedure for the correction of exstrophy (in this or other institutions). In 2, there had been 4 prior operations for this anomaly (Table I).

Types of previous surgical procedures. Anterior reconstruction of the bladder and abdominal wall with techniques similar to those described by Young,[10] Sweetser,[8] and Swenson,[9] were initially employed in all except one of these patients (3 in other institutions). Two such attempts were made in 1 child, and 3 (anterior reconstructions) in 2 others. These procedures resulted (except in 1 instance) in the formation of a solid, cosmetically satisfactory anterior abdominal wall over the reconstructed bladder. True continence, however, was never achieved and partial continence only when accompanied by some degree of bladder outlet obstruction.

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*Four of these patients are included in the present study (Table I, Nos. 2, 4, 5, and 6.)

Table I. *Vesicoileosigmoidostomy in exstrophy of the bladder*

Sex and present age	*Associated anomalies*	*Previous operations for exstrophy (age)*
Case 1,* female, 2 yr.	Left renal agenesis, imperforate anus, absent digit (prematurity)	Plastic reconstruction of "urethra" (only), 6 months
Case 2, female, 4 yr.	Ureterectasis (right) noted on initial urogram at 18 mo., "megaloureter"	Anterior plastic reconstruction, 18 mo.; bladder enlargement with isolated ileal segment and anterior reconstruction, 3 yr.
Case 3, female, 6½ yr.	None	Anterior plastic reconstruction, 2½ yr.; anterior plastic reconstruction, 3½ yr.; anterior plastic reconstruction, 4½ yr.
Case 4, female, 5 yr.	None	Bladder enlargement with isolated ileal segment, 3 yr.; anterior plastic reconstruction, 4 yr.
Case 5, female, 7½ yr.	Rectal prolapse from age 3 wk.	Anterior plastic reconstruction; 2½ yr.; bladder enlargement with isolated colon segment, 4½ yr.; anterior plastic reconstruction, 5½ yr.; anterior plastic reconstruction, 6½ yr.
Case 6, male, 6 yr.	None	Anterior plastic reconstruction, 9 mo.; bladder enlargement with isolated colon segment, 2½ yr.; anterior plastic reconstruction, 3½ yr.; anterior plastic reconstruction, 5 yr.

*Cases 1, 2, and 3 have been referred to in a prior publication.[5]
†Serum chloride determination 119 mEq./L. at 2 months, decreased to 102 mEq./L. at 6 months postoperatively.

In addition to anterior reconstruction, in 4 patients the rudimentary bladder had previously been enlarged with isolated intestinal segments. In 2 of these, ileal segments had been employed. In 2 others, a segment of sigmoid colon had been used to enlarge the bladder and form a conduit to the perineum.[3] In the latter, stenosis of the distal end of the sigmoid conduit had occurred.

In 1 case an attempt to form an anterior urethra with a pedunculated flap of bladder wall, as a preliminary step toward vesical closure, had been the only prior procedure utilized.

The growth curves (height and weight) in 3 of the children were within the normal range.* In 3 others, including 2 of those with additional major genitourinary tract disease, a regularly ascending growth curve was found, but with a low starting point and a maintained depression, largely below the second percentile.

Completely satisfactory control of defecation had been achieved in all but one, the youngest (Case 1), including the girl with early rectal prolapse. After the anterior plastic procedures noted, the children were no longer subject to the constant irritation

*State University of Iowa standard curves.

Preoperative status	*Age at time of this procedure*	*Postoperative status*
Bladder interior exposed; prompt excretion (right) slight ureterovesical narrowing (right) on I.V.P.; NPN 27 mg.%; no abnormalities of serum electrolytes	15 mo.	Anterior bladder closure intact; urinary (and fecal) continence satisfactory for age; I.V.P. unchanged (1, 2, and 6 mo.); NPN not elevated (1, 2, and 6 mo.); serum electrolytes unchanged (1, 2,† and 6 mo.)
Bladder interior exposed, anemia secondary to chronic blood loss; prompt excretion ureterectasia (bilateral), no obstruction on I.V.P.; NPN 35 mg.%; no alteration in serum electrolytes	3 yr., 9 mo.	Anterior bladder closure intact; partial urinary continence; I.V.P. unchanged (1 and 3 mo.); no NPN elevation (1 and 3 mo.); serum electrolyte levels unchanged (1 and 3 mo.)
Anterior bladder closure intact; total urinary incontinence; prompt excretion, normal structure of upper tract on I.V.P.; NPN 30 mg.%; no alterations in serum electrolytes	6 yr., 6 mo.	Anterior bladder closure intact; urinary continence at night (daytime stress incontinence); I.V.P. unchanged (1 mo.); NPN not elevated (1 and 3 mo.); serum electrolyte levels unchanged (1 and 3 mo.)
Anterior bladder closure intact; total urinary incontinence; prompt excretion, normal structure of upper urinary tract on I.V.P.; NPN 17 mg. %; no alterations in serum electrolytes	5 yr.	Anterior bladder closure intact; urinary continence complete; I.V.P. unchanged (1 mo.); NPN 14 mg.% (1 mo.); serum electrolyte levels unchanged (1 mo.)
Anterior bladder closure intact; total urinary incontinence; prompt excretion, normal structure of upper urinary tract on I.V.P.; NPN 21 mg.%; no alterations in serum electrolytes	7 yr., 6 mo.	Anterior bladder closure intact with anterior vesical fistula; rectal continence for urine and feces satisfactory; I.V.P. unchanged (1 mo.); NPN 20 mg.% (1 mo.); serum electrolyte levels unchanged (1 mo.)
Anterior bladder closure intact; total urinary incontinence; prompt excretion (bilateral), calyectasis and ureterectasis without obstruction (right) on I.V.P.; NPN 22 mg.%; no alterations in serum electrolytes	6 yr.	Anterior bladder closure intact; urinary continence satisfactory; I.V.P. unchanged (1 mo.); NPN 25 mg.% (1 mo.); serum electrolytes unchanged (1 mo.)

of an exposed bladder surface, and from the point of view of the parent, their only real disability was urinary incontinence.

Three of the patients (Cases 1, 2, and 6) had grossly abnormal excretory urograms. Two had been noted from the time of initial examinations and the third had developed during the course of previous anterior reconstructions (Table I). In addition, in Case 1, the right ureteropelvic junction seemed slightly narrowed in studies performed immediately prior to the definitive procedure. Each of the remaining patients had serial intravenous pyelograms performed before, during, and after the preliminary operative procedures described (Table I) with normal excretion demonstrated and no alterations in the structure of the upper urinary tract.

Determinations of serum nonprotein nitrogen and electrolyte concentrations (sodium, potassium, chloride, and carbon dioxide) were within the usual range in all of the children prior to operation.

TECHNIQUE OF THE OPERATIVE PROCEDURE

The operation was performed through 2 incisions, (1) an initial superior transperitoneal approach and (2) a secondary, extra-

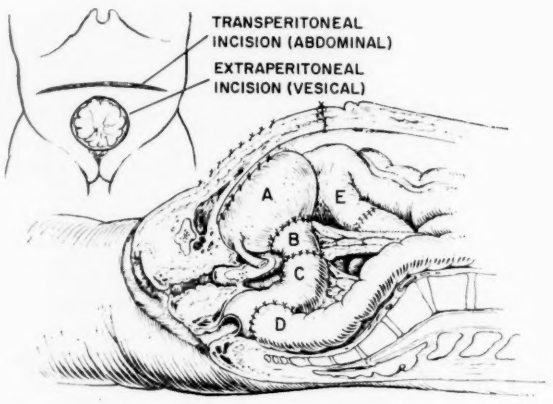

Fig. 1. Vesicoileosigmoidostomy. *A,* Urinary bladder after anterior closure. *B,* Isolated ileal segment with anastomosis to the bladder and colon. *C,* Sigmoid colon segment utilized as a urinary conduit. *D,* Sigmoid colon (functional intestinal tract). *E,* The terminal ileum after end-to-end anastomosis.

peritoneal dissection about the rudimentary bladder.

In only one of the present cases was the exstrophy in an approximately natural state, and the form of the second (vesical) incision depended upon the type of previous procedure employed. In all, however, the bladder was widely opened anteriorly (if not open), and an extensive mobilization of lateral vesical walls performed.

The superior approach was made uniformly through a wide, transverse lower abdominal incision with division of both rectus muscles. This operative field was kept separate from, and lay 2 to 3 cm. superior to, the incision about the exstrophied bladder (or its reconstruction).

The intra-abdominal procedure may be divided into 4 steps, (1) separation of the colon to form divided fecal and urinary conduits, (2) isolation of an ileal segment, (3) connection of the "urinary" colon conduit and ileal segment utilizing a valve-like (ileal "nipple") anastomosis, and (4) connection of the ileal segment to the posterior wall of the bladder.

The initial step was accomplished by transection of the colon approximately 10 cm. above the pelvic floor. The proximal end of the divided colon was then brought down to a position immediately above the peritoneal reflexion where an end-to-side anastomosis was performed between the end of the proximal segment and the side of the distal colon. A routine 2-layer anastomosis by an "open" technique with internal, continuous absorbable sutures supported externally by interrupted nonabsorbable sutures was employed. This provided a diverticular intestinal segment for use as a urinary conduit.

The second step consisted of isolation of a segment of terminal ileum with intact mesentery by the usual techniques. This segment should be 8 to 10 cm. in length, and lie approximately 10 cm. proximal to the ileocecal junction. Intestinal continuity was re-established by end-to-end anastomosis.

In the third step the distal end of the isolated ileal segment was opened and the serosa removed or scarified for 2 cm. from the distal margin of transection. The mucosa and submucosa were then everted and sutured to the margin of the intact serosa proximally with fine absorbable sutures. This formed a "nipple" of mucosa-covered ileum, 1 cm. in length. This technique is similar to that used in forming an ileostomy stoma on the anterior abdominal wall. The nipple of ileum was then introduced into the open end of the distal colon segment where it projected into the lumen for approximately 1 cm. (Fig. 2). A serosa-to-serosa closure between ileum and colon was formed around the base of the ileal nipple with nonabsorbable sutures.

The fourth step was performed through both the abdominal and the vesical incisions. It was preceded by reflexion of the peritoneum from the posterior vesical wall and mobilization of the superior and posterior aspects of the bladder. The ureters were identified and dissection carried between them. An opening was made in the pelvic peritoneum and in the base of the left broad ligament (in the female) for the passage of the conduit to the bladder.

Anastomosis between the proximal end of the ileal segment and the vesical wall was begun within the bladder. A vertical incision

was made in the posterior wall between the ureteral orifices, extending superiorly for approximately 2 cm. Into this opening the proximal end of the isolated ileal segment was inserted. The ileal mucosal layer was sutured to the vesical mucosal and muscular wall with fine, interrupted absorbable sutures placed throughout the circumference of the bladder opening (Fig. 3). Through the peritoneal incision, the ileal seromuscular surface was then approximated to the advential wall of the bladder with interrupted nonabsorbable sutures. The margins of the peritoneum were also sutured to the ileal wall where the latter passes through the peritoneum toward the vesical anastomosis.

The final phase began with completion of the mobilization of the exstrophied bladder wall. If not previously accomplished, a division of the skin margins was continued inferiorly about the edge of the bladder mucosa. The full thickness of bladder wall was then freed from surrounding tissues both laterally and inferiorly (the superior and posterior aspects had been previously elevated). Only the vascular pedicles about the ureteral openings remained after this dissection. The bladder was then closed anteriorly and inferiorly with a double row of absorbable sutures. This was facilitated by the relaxation which results from the introduction of the ileal segment into the posterior wall. If the bladder mucosal area is quite small, it may be necessary to enlarge it with an intestinal segment as a preliminary operative procedure.[3] A large catheter was passed from the side of the reconstructed bladder through the anterior abdominal wall.

The abdominal procedure was completed by the closure of the 2 mesenteric defects (ileal and colonic) and approximation of the combined ileocolonic segment to posterior peritoneal surfaces. It may be possible to place all or a part of the conduit segment (ileum and colon) in an extraperitoneal space posterior and superior to the bladder.

Abdominal closure was made in layers. The peritoneum was usually intact and could be closed with continuous sutures. The fascial layers of both incisions were approximated with interrupted sutures of steel wire (No. 30) and the subcutaneous fascia with absorbable sutures. In the female the cli-

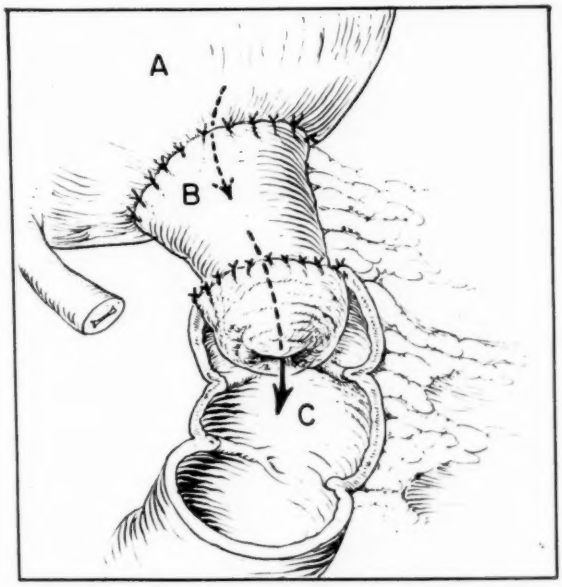

Fig. 2. Detailed study of the ileal nipple formed at the anastomosis between the isolated ileal segment *(B)* and sigmoid urinary conduit *(C)*. The ileal segment is shortened for diagrammatic clarity. Its actual length after eversion of the distal end to form the nipple is 6 to 7 cm.

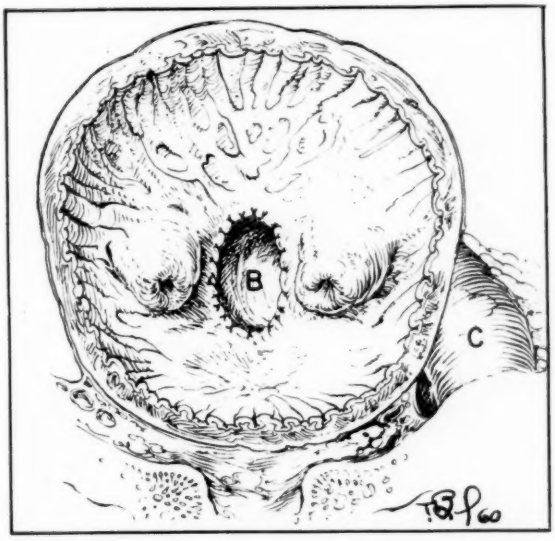

Fig. 3. Anterior view of the interior of the bladder after anastomosis of the isolated ileal segment *(B)* to the vesical wall between the ureteral orifices. *C,* Sigmoid colon.

toris was formed by uniting its 2 halves in the midline and the vulva was further reconstructed by mobilization and closure of laterally placed tissues. In the male the genital openings were left intact for subsequent penial reconstruction.

Preoperative preparation for this procedure has included a regimen of orally administered neomycin, catharsis, and enemas for 2 days. Bladder drainage by anterior abdominal wall catheters has been maintained for 2 weeks postoperatively in all patients.

IMMEDIATE AND SHORT-TERM EVALUATION OF EFFECTS OF VESICOILEOSIGMOIDOSTOMY

There has been no death associated with this procedure. The postoperative period of study of these patients has been short, averaging 3 months, with the longest of 8 months' duration.

Temporary anterior vesical fistulas have developed in 2 children. One has closed spontaneously.

In addition to exstrophy, 3 patients upon whom this procedure was employed had major structural alterations in the upper urinary tract, unilateral renal agenesis and ureterectasia (possible megaloureter), without mechanical obstruction in 2. These patients were not azotemic, and their postoperative status was not altered in this regard. Azotemia and hyperchloremia were reported to have developed in Patient 1 during a severe febrile illness in another city 4 months after operation. There was no laboratory evidence of either state when the patient was evaluated subsequently in this institution. An elevation of serum chloride levels to 119 mEq. per liter was noted in the same patient 2 months after our operation, but a normal level (102 mEq. per liter) was found 4 months later.

In the remaining patients, intravenous pyelography has shown no alteration in excretory function or structure of the upper urinary tract and results of nonprotein nitrogen determinations have always been within normal limits. No evidence of hyperchloremia or other deviations from expected serum electrolyte concentrations have been observed.

As might be anticipated from the results obtained in children with ureterointestinal transplants, the voluntary control of urinary outflow through the rectum has been generally, although not completely, satisfactory. The youngest child (Case 1), age 2 years, is the only patient in the series in whom partial control is still in doubt.

Cystograms performed in 3 patients after operation showed a prompt passage of contrast material to the rectum. In one, a delay in emptying was followed by a sudden and complete bladder evacuation, possibly secondary to a bladder contraction.

A barium enema study in 2 patients showed apparent competence of the ileosigmoid anastomosis to the barium solution, as the pressures employed were sufficient to cause filling of the colon diverticulum (and the remaining colon), but not of the bladder (Fig. 4). The ileal nipple may be viewed with a proctoscope and the bladder catheterized.

DISCUSSION

Upon review of the procedures employed by American and European surgeons for exstrophy prior to the adoption of ureterointestinal transplants, it seems that every conceivable anastomotic arrangement of the ureters, bladder, colon, rectum, and ileum had been attempted. The technique described here (vesicoileosigmoidostomy) includes some elements of operations originally reported as early as 1903 (Borelius[2]) and 1907 (Berg[1]) with adaptation described as recently as 1958 (Snyder[7]). To credit even major contributors in this field of lower urinary tract reconstruction would require monograph form.[6, 10] The combined features of the vesicoileosigmoidostomy technique, however, have apparently not been previously employed.

The rationale behind the adoption of this complicated operative technique was based on the apparent desirability of including certain features in the reconstruction of the

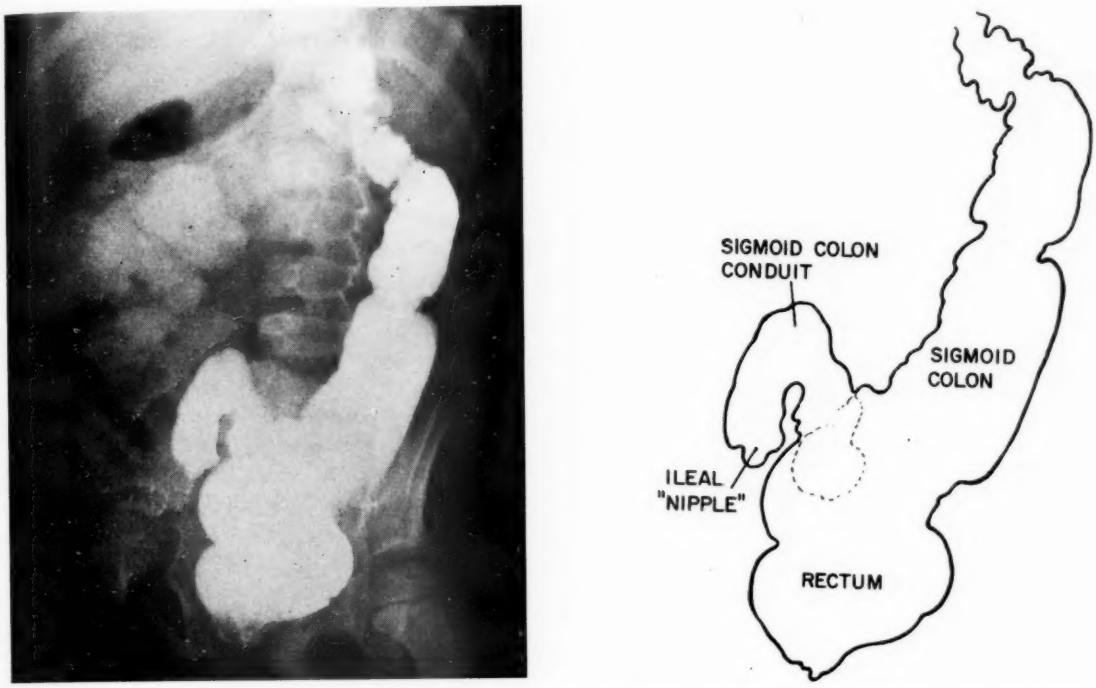

Fig. 4. Roentgenographic study with barium emulsion under usual pressure (36 inches) passing into the colon and urinary conduit, but not into the ileal segment or bladder.

bladder and its outflow tract. These included (1) preservation of the ureterovesical junctions, (2) anterior vesical closure to form a urinary reservoir, and (3) formation of a conduit between the reconstructed bladder and the rectum, with sufficient valve-like activity to prevent gross fecal contamination of the vesical cavity.

It has been regarded as advantageous to preserve the ureterovesical junction as a deterrent to ascending infection in the urinary tract. Theoretically, the bladder is a more desirable urinary reservoir than the rectum or colon because of the absence of absorptive activity in the mucosa. Under these circumstances, unfortunately, it may also act as a source of stasis and recurrent infection, although this has not been apparent in our series to date.

Whether the bladder will actually function as a reservoir or simply as a conduit when connected by the operative technique described is uncertain.

The conduit between the bladder and the rectum has been formed from 2 intestinal segments, ileum and sigmoid colon, in order to minimize the length of ileum utilized and facilitate construction of a valve-like anastomosis which would keep solid fecal material in the colon segment. The "valve" is simply a projection or nipple of ileum which protrudes into the colon lumen. This was placed in a colon diverticulum rather than in the sigmoid colon itself to avoid the intestinal complications of partial obstruction or intussusception.

It is recognized that the worth of an innovation such as this in the treatment of exstrophy must be determined by an assessment of its effectiveness over several decades. Specifically, one wonders if it can provide more protection to the renal reserve of the child than does standard sigmoid ureterointestinal anastomosis. Although theoretical arguments as to why it may, or may not, provide protection from renal infection of intestinal origin are of interest, there is probably no way to determine the answer to this question except by clinical study.

This basic procedure might be modified to include the transplantation of the ureters

to the ileal segment in the management of vesical carcinoma, and so forth, when cystectomy is required.

SUMMARY

A technique of bladder reconstruction and formation of a vesical outflow tract to the rectum for the management of exstrophy is described. In this procedure an isolated ileal segment and a partially divided sigmoid colon conduit are utilized. The union of the ileal and colonic elements of the urinary drainage tract is made in a valve-like anastomosis to minimze fecal regurgitation into the re-formed bladder. Six patients in whom this technique has been employed have shown no evidence of renal impairment or significant alterations in serum electrolyte concentrations during the immediate postoperative period. They appear to have a high degree of urinary continence. A long-term evaluation of this procedure as a substitute for ureterointestinal anastomosis in patients with exstrophy of the bladder seems warranted.

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Surgical treatment of bowel and bladder dysfunction in a case of spina bifida with meningomyelocele

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Congenital and acquired lesions of the lumbosacral spine may result in incapacitating bowel and bladder dysfunction in addition to the more obvious musculoskeletal deformities. The most common congenital lesion which affects the lumbosacral nerve roots is spina bifida cystica. Spina bifida is said to occur once in every 1,500 births.[6] Disturbances of the lumbosacral nerve roots usually produce bowel and bladder symptoms recognizable in infancy, but, as in diastematomyelia, patients may experience no dysfunction until linear growth advances to such a degree that traction produces neural injury. Trauma or neoplasia similarly may result in the onset of symptoms.

The consequences of these neurological disturbances on both micturition and defecation have been well documented. Urologic problems associated with spastic paraplegia have been discussed by Bors,[1-3] Bors and Comarr,[4] and by Hutch,[12] while those associated with flaccid paraplegia of spina bifida have been summarized by Kennedy and Hodges[14] and by McCarthy and Lindsay.[15] Stolov[21] and Bumpus and associates[5] have reviewed the urologic complications which result from spinal injuries.

The influence of spinal abnormalities on rectal function and the evacuation reflex were summarized by Guttman[11] in a symposium on rectal incontinence. Swenson[22] has pointed out the possible importance of a lack of normal sacral sensation in the constipation seen in patients with meningomyelocele. The experimental evidence of the relationship of sacral neurological lesions to bowel dysfunction has been shown by the work of Scott,[18] Schlitt,[17] and Denny-Brown.[8] Experimental studies relating these lesions to bladder dysfunction have been reported by Jacobson[13] and by Shoemaker.[19, 20]

The possible operative approaches to the problems have been discussed by Gross,[10] Emmett,[9] and Thompson.[23] Permanent diversion of either the urinary or the fecal stream has been considered as only a last resort.

Since World War II much has been written concerning the management of the visceral dysfunction of spastic paraplegia of military and of civilian patients.[16] An aggressive and coordinated approach can be applied also to the treatment of the visceral dysfunctions associated with flaccid paraplegia, particularly since many of the individuals with this condition are of normal mental development.[10]

A case history is presented as illustrative of the rewarding outcome of such a coordinated and aggressive approach.

CASE REPORT

G. B. M., a 15-year-old white male high school student was first seen with gross hematuria associated with suprapubic pain of 24 hours' duration.

The patient had been the product of a full term, uncomplicated pregnancy with spontaneous delivery. At birth he was found to have a lumbosacral spina bifida cystica. A neurosurgical con-

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sultant advised then, and later, that exploratory operation was not indicated. The patient was in a hip spica from the age of 20 months to 24 months for reduction of a congenital dislocation of the left hip, with a satisfactory result. Prior to this he was said to have had spontaneous bowel movements, but subsequently obstipation developed which necessitated enemas 2 to 3 times per week. Over the next 12 years the regular enemas became progressively more arduous until 2 to 5 hours was required to accomplish each irrigation and often the evacuation was not completed until several hours later. There was otherwise no fecal soiling.

Diapers had been necessary throughout the patient's life because of total urinary incontinence. There had been a single episode of urinary tract infection when he was 3 years of age, but otherwise there had been no symptoms of urinary tract disease. The patient had apparently had normal erections and emissions since the onset of puberty.

Mental development had been excellent and the patient's academic accomplishment had been superior despite his physical handicaps.

There was no family history of congenital deformity or of neuromuscular disease, and the one younger male sibling was normal. When admitted, the patient had recently undergone a triple arthrodesis and tendon transplantation for correction of an equinovarus deformity of the left foot, with good functional result.

Physical examination. The blood pressure was 110/80 mm. Hg. The abdomen was unremarkable except for an enlargement of the bladder extending midway to the umbilicus. On the back, beneath an area of hypertrichosis, a soft 12 by 14 cm. mass was present, overlying the sacrum and left gluteal regions. The genitals were normal. Slight tone was present in the external anal sphincter. The ampulla was filled with firm feces. The prostate gland and seminal vesicles were normal. Bimanual examination confirmed the enlargement of the urinary bladder. Good voluntary levator ani muscle contraction was present.

Neurological examination. The gait was abnormal with a marked limp in favor of the shortened left leg. Results of the Romberg test were negative. The musculature of the trunk, superficial abdominal reflexes, and trunk sensation were normal. In the left leg, which was shorter than the right leg by a half inch, there was marked atrophy of all muscle groups. The thigh muscles on the left were involved to a greater extent than the muscles of the lower leg and foot, and there was marked underdevelopment of the left gluteal group. The knee jerks were active and equal. The ankle jerks were absent. There was complete anesthesia and analgesia involving the perianal area and the posterior aspect of the right thigh to the popliteal space. A wide band of hypesthesia and hypalgesia extended across the left buttock and down the entire posterior surface of the left leg and over the lateral dorsum of the foot.

Laboratory tests. The hemoglobin was 13.0 Gm., white blood cells 12,500, polymorphonuclear neutrophils 77, eosinophils 1, and lymphocytes 22. Urinalysis showed the urine to be red in color. Its character was cloudy, specific gravity 1.020, pH 7.5, and albumin 4+. Sugar was negative, red blood cells innumerable, white blood cells innumerable, and there were no casts. *B. proteus*, sensitive to chloramphenicol, chlortetracycline, oxytetracycline, and nitrofurantoin, was cultured from the urine. The nonprotein nitrogen was 30 mg. per cent.

Roentgenographic reports. No calculi were noted on the excretory urogram. There was an abnormality of the lumbar spine and sacrum. Bilateral ureteropyelocalycectasis was present. Cystography showed a contracted bladder with a marked degree of trabeculation with deep cellules throughout. No vesicoureteral regurgitation was demonstrated.

Hospital course.

First admission. At the time of entry to the hospital the residual urine was equal to the total bladder capacity of 200 ml. and an inlying urethral catheter was left for straight drainage. The urinary infection was treated with nitrofurantoin. Cystoscopy under anesthesia disclosed a normal vesical neck and ureteral orifices. There was no apparent ureteral efflux. A cystometrogram was consistent with an autonomous neurogenic bladder with a voluntary voiding effort on 90 mm. Hg of Credé pressure.

A transurethral resection of the vesical neck was carried out under general anesthesia with the hope of reducing the outflow resistance and relieving the urinary retention and overflow incontinence. The urethral catheter was removed on the third postoperative day. There was slight dribbling of urine for 24 hours, but the patient has since voided a good stream with Credé compression and has remained completely continent of urine.

Initial bowel investigation was begun during this hospitalization and the patient was discharged on the eleventh postoperative day in good condition and voiding well.

Second admission. On the fifteenth postoperative day the patient was readmitted with urinary tract bleeding which was controlled by inlying catheter drainage.

Third admission. Fluoroscopy of the colon with barium enema showed normal peristalsis of the transverse colon, but a lack of peristalsis throughout the left colon, which was dilated. There was no "spastic area" to suggest an aganglionic mega-

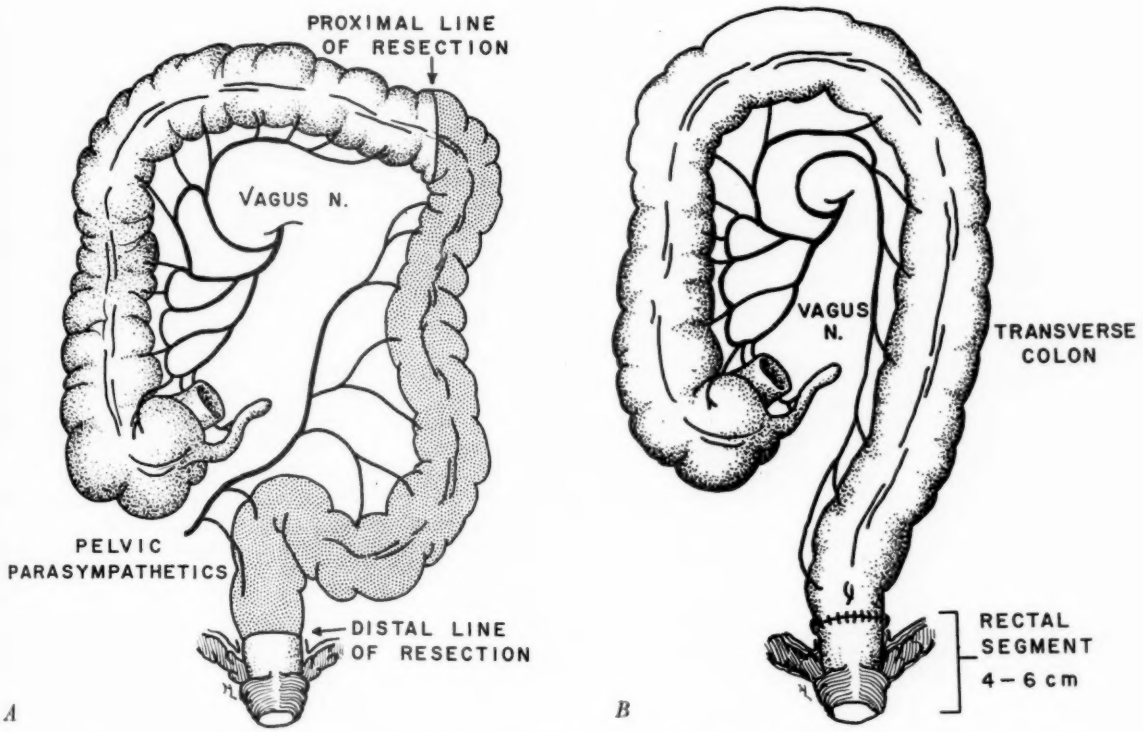

Fig. 1. *A*, Preresection and *B*, postresection diagrams of colon which show limits of resection for elimination of the sacrally innervated colon. Only a 4 to 6 cm. rectal segment is left.

colon or Hirschsprung's disease, but rather a general hypotonia of the left colon and rectum with no coordinated propulsion. Balloon studies demonstrated normal peristaltic activity in the transverse colon, but little spontaneous activity in the sigmoid or rectum. With distention of the balloon discomfort was experienced only in the transverse colon, with complete absence of a sensation of fullness in the sigmoid and descending colon. A diminished but definite contraction of the external anal sphincter was elicited. Levator ani contraction was strong. A trial of medical management, consisting of Prostigmine and pentolinium tartrate (Ansolysen) administration and enemas, was initiated. This and other systems of medical therapy, which were carried out at the patient's home over the next 3 to 4 months, were unsuccessful in eliminating the need for regular and prolonged enemas.

Fourth admission. The patient was readmitted for left colon resection. The bowel was prepared with saline irrigations, succinylsulfathiazole, and neomycin. On visualization the left colon appeared abnormal. It was tubular, thickened, and uniform in size. Peristaltic waves were absent on stimulation. Peristaltic activity of the transverse colon, by contrast, was normal. The left colon was resected beyond the last arcade from the superior mesenteric artery, and a pull-through rectocolic anastomosis was performed, preserving the last 4 to 6 cm. of the rectum (Figs. 1 and 2). The resection was performed proximal to the level of resection usual in a Swenson procedure in order to compensate for the deficient external anal sphincter. Microscopic examination of the 32 cm. resected segment of colon and rectum showed ganglion cells to be present throughout the specimen.

After a rectal irrigation on the fourth postoperative day, the patient defecated involuntarily for the next 6 days. Fecal continence, with only periodic soiling, began on the tenth postoperative day. Voluntary control, without soiling, was attained over the next 4 weeks.

Postoperative urinary retention was managed by inlying catheter drainage for 1 week. After the removal of the catheter, attempted evacuation of either the bowel or the bladder resulted in simultaneous evacuation of both. Differential control was attained gradually over a 6-week period.

Over the 2½-year period during which the patient has been followed after colonic resection, the bowel function has remained very satisfactory. During the past year he has passed 1 to 2 stools per day without any complicating impactions. He attended school without difficulty, and soiled only once or twice during the entire year. For approximately 1 year he employed a small saline irrigation in the morning to facilitate a bowel

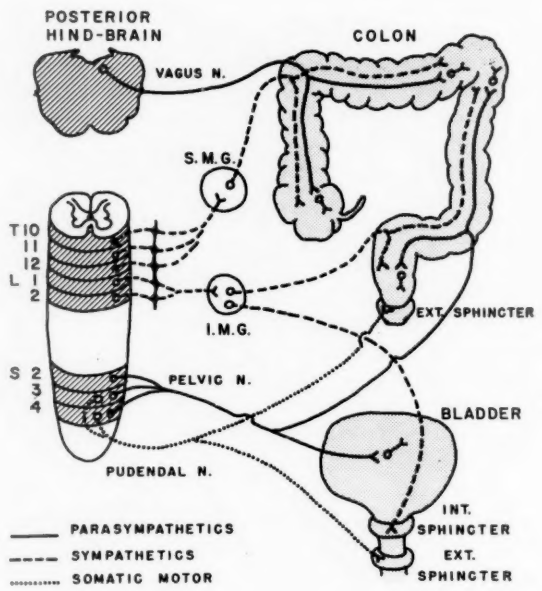

Fig. 2. Autonomic and somatic motor innervation of the lower bowel and bladder.

movement before school, but has found that even this is no longer necessary. A roentgenogram taken after a barium enema 1 year after resection showed no dilatation of the colon above the anastomosis. With the exception of an occasional episode of cystitis, readily controlled with chemotherapy, the patient has had no urinary difficulties. He carries no residual urine, and a recent intravenous pyelogram shows the kidneys to be normal.

The improvement in this patient's personal outlook and his release from a dependency upon his parents has been particularly impressive. Although he has not been given normal function of bowel or bladder, the improvement has been unquestionably beneficial.

DISCUSSION

A combined evaluation and therapeutic approach to conditions of this type by the many disciplines concerned offers maximal possibilities for rehabilitation. As shown in Fig. 3, the left colon and the rectum, the bladder, and the sphincters of the urinary and the gastrointestinal tract depend upon intact innervation from the sacral region. Lesions in this area may result in widely varying dysfunction. The resulting failure of either the lower gastrointestinal tract or the urinary tract to function normally leads to a proximal decompensation. If function is to be restored toward normal, the defectively innervated portion must be repaired, bypassed, excised, or replaced with a normally innervated substitute.

Management of the urinary tract depends upon a thorough assessment of the structural condition of all of the component parts of the urinary system as well as the functional integrity of the entire system. If decompensation has occurred, a period of drainage which is sufficient to allow restoration of optimal renal function is necessary before definitive correction can be initiated.

Procedures to decrease outflow resistance as utilized in our patient are effective only if the detrusor force of the defectively innervated bladder, and increased intra-abdominal pressure, will produce voluntary bladder emptying. Measures to increase detrusor force should be combined with reduction of the outflow resistance. When a segment of bowel is used for detrusor force in a cystoplasty, it must be normally innervated, and use of the left colon may be contraindicated in cases in which sacral neurological deficit exists. Apparent incontinence should not necessarily contraindicate operation to reduce outflow resistance.

The bowel dysfunction secondary to sacral nerve defects can in most instances be managed well by thorough and persistent nonoperative measures (daily enemas or colonic irrigations, diet, and use of suppositories), all of which aim at the development of regular and complete emptying of the colon. In some instances, as in our case, these measures fail to evacuate the colon or become so involved and time consuming as to pose a serious handicap to the patient. In this case excision of the defectively innervated colon improved function considerably. While improvement after such a resection may be related to the increased liquidity of the stool passed, as Davis[7] suggests in advising resection for dolichocolon, it appears in this case that the ability of the bowel to respond to stimuli and to have more normal propulsive force is of equal or greater importance. To our knowledge the

possibilities of such resection of the defectively innervated colon in this group of patients have not been previously realized. Even if colonic irrigations were necessary, the advantages of dealing with a normally responsive bowel as contrasted with an inert one are obvious. Improvement of continence with a marginally functioning sphincter muscle is greatly enhanced, as in our case, with the elimination of impaction and "fecal decompensation." As with the urinary tract, permanent diversion should be reserved for failures of a more direct approach.

SUMMARY

In patients with bladder and bowel dysfunction resulting from lumbosacral neurological deficits, an aggressive and dynamic attempt should be made to secure the maximal improvement toward normal. Many of the patients with normal to superior intelligence are crippled primarily by the limitations imposed by bowel or bladder dysfunction. In such patients the lower urinary tract and the left colon, which derive their innervation from the diseased spinal area, lack normal sensation and motor innervation to varying degrees. Although conservative nonoperative management may suffice, when decompensation occurs or if nonoperative management imposes crippling limitations, surgical approaches are indicated. Resection of the defectively innervated colon can be performed, and a normally innervated segment of colon anastomosed to the rectum. Reduction of outflow resistance in the urinary bladder by transurethral resection or vesical neck revision allows for more adequate bladder emptying by detrusor force and Credé pressure. With these measures, utilization of available structures is attempted for a more anatomic means of improving function.

Such a program appeared necessary in the case of a 15-year-old boy with a lumbosacral myelomeningocele with a lifelong history of obstipation and urinary dribbling. The dramatic changes in bowel function and urinary function have changed this patient's outlook and adjustment to society.

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Duodenal closure after gastrectomy for duodenal ulcer

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In February, 1956, we reported preliminary results of a method for duodenal closure after gastrectomy for the large ulcer of the posterior wall of the first part of the duodenum.[1] This was a modification of a method recommended by Nissen[3] for the duodenal closure when a pancreatic duct entered the base of the ulcer. When there was no pancreatic duct opening, Nissen used both the proximal and distal margins of the ulcer for the closure. With our method the distal margin is not utilized and it has not been found necessary, in many cases, to use the proximal margin of the ulcer. When the duodenal wall is absent, sutures are placed in the pancreatic capsule and scar tissue adjacent to the ulcer edge. This method requires a fairly pliable, well-vascularized anterior duodenal wall.

With this technique, as the dissection is carried posteriorly distal to the pylorus, the ulcer may be intentionally entered and the contiguous duodenal wall trimmed and excised as indicated. Thick, indurated, and edematous duodenal wall proximal and adjacent to the ulcer may be removed as long as the duodenal wall along the upper and lower borders of the duodenum is retained. Enough anterior wall should be left to permit easy closure without undue tension (Fig. 1, *A*).

The closure is accomplished with 2 or 3 layers of interrupted No. 4-0 silk. The sutures on the pancreatic side are placed superficially in a Lembert fashion. Adequate bulk of tissue for proper support can be obtained by taking multiple bites in a diagonal fashion as shown in Fig. 1, *B* and *C*. Near the ulcer crater, the seromuscular layer of the duodenal wall may be incorporated in the sutures. Frequently, near the upper and lower borders, the posterior sutures can be placed in the duodenal wall alone. By placement of the sutures superficially into the pancreas, the hazard of deep penetration into the head of the pancreas is avoided. On the anterior duodenal side, Lembert or Cushing mattress sutures have been used, depending on the width of the wall which has to be turned into the lumen. Frequently a more satisfactory closure is made when the sutures in the anterior wall are seromuscular rather than full-thickness. If a bleeding vessel is present in the base of the ulcer it is secured by figure-of-eight sutures of No. 2-0 silk.

It is obvious that this method of duodenal closure is not necessary when the ulcer is on the anterior surface of the pancreas and adequate length of duodenal wall is present beyond the ulcer which can be readily freed without dissection into pancreatic tissue. In that situation the ulcer can be exteriorized.

Since the original publication, use of the special technique for duodenal closure has been continued at the Providence Veterans Administration Hospital and has been introduced at the Bronx Veterans Administration

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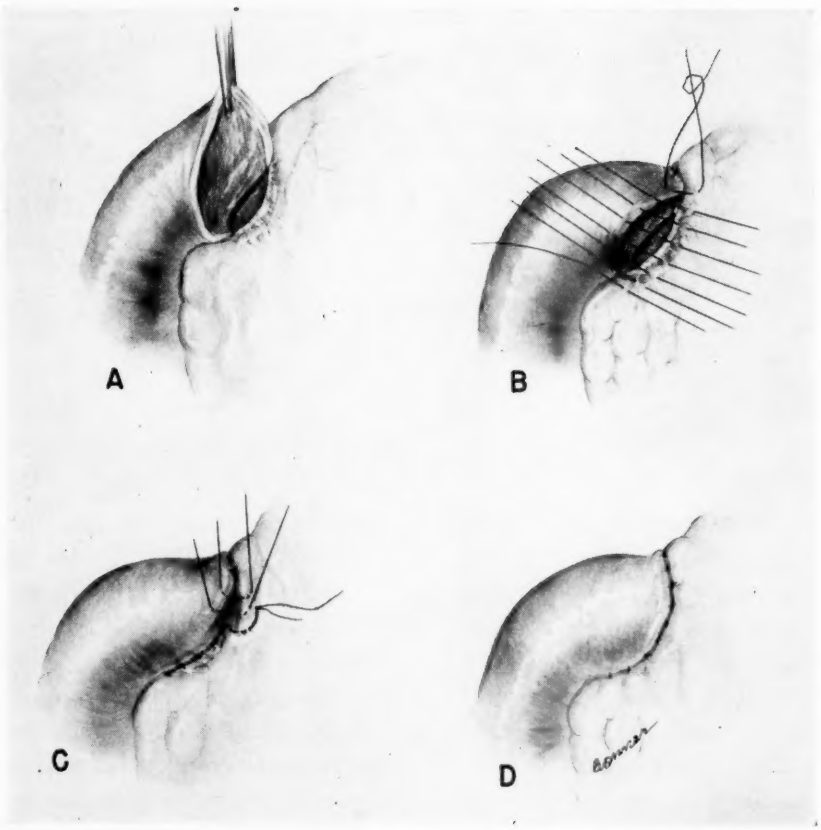

Fig. 1. *A*, Ulcer crater is entered and the posterior and anterior wall of the duodenum excised as indicated. *B*, First layer of sutures is inserted. *C*, Second layer of sutures is being inserted. Note diagonal placement of suture with multiple bites of tissue. *D*, Completed closure.

Hospital. At the former hospital[2] it has been found advisable to utilize this method in 109 of 699 duodenal closures. There was only 1 duodenal complication in the 109 cases. This occurred when the duodenum was extensively involved with ulcer and the anterior duodenal wall was thickened. The duodenal fistula closed spontaneously. At the Bronx Veterans Administration Hospital the method has been used on approximately 25 occasions with no duodenal stump complications.

This method allows a safe and rapid dissection of the duodenum and incision of or trauma to the pancreas is avoided. The dissection must be carried out meticulously and adequate blood supply of the duodenal wall retained. If one is concerned about the security of the closure a Penrose drain may be inserted near the duodenum. As one gains experience with this method the drain is rarely utilized.

CONCLUSION

The technique and results of a method for duodenal closure after gastrectomy for the large posterior ulcer of the first part of the duodenum are reviewed. This method has been found to be safe and secure if performed according to the recommended technique.

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Historical views of the ideal surgeon

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There have been but few instances in history when the medical community has been in as glaring a limelight as it is at present. Divested of much of the semiprotective veneer of mysticism with which it was formerly cloaked, it is now under close scrutiny from both within and without. Those who would see organized medicine as we know it flourish recognize that this is only possible by providing an ever-demanding laity with physicians of the first rank, both in training and comportment. In an age when the Decalogue of Mount Sinai and the Golden Rule are relegated to the Sunday school, the reaffirmation of basic principles becomes essential for survival. Educators have become more keenly aware that the student of medicine, who is exposed to a formal course of medical ethics only under unusual circumstances, and pledges his troth to mankind and his profession merely by a monotone recitation of the Oath of Hippocrates at graduation, may require more intensive inculcation. Hence, there has been a recent resurgent concern and promulgation by several regional and national medical associations of diverse codes of ethics and requirements of aptitude and behavior.

It is interesting to review the opinions of some of the early fathers of Surgery concerning the precepts governing the ideal practitioner of their craft. These concepts went much further than to require of him the oft-quoted "eye of an eagle, heart of a lion, and hand of a woman."

One can start with the Hindu surgeons, Sushruta and Charaka. They lived in the period of Indian history called the Vedic epoch after the four *Vedas,* or sacred writings, of the ancient East which constitute the glory of Sanskrit language and literature. Sushruta and Charaka wrote extensive treatises on surgery and medicine called *Samhitas.*

The *Sushruta-Samhita,* circa 600 B.C., states, "Surgery is the first and highest division of the healing art, least liable to fallacy, pure in itself, perpetual in its applicability, the worthy product of heaven, the sure source of fame on earth."

But it stresses the value of all-around training and knowledge of Medicine, and of study as well as factual practice when it says, "He who knows only one branch is like a bird with one wing . . . but he who combines reading with experience proceeds safely and surely like a chariot on two wheels."

There is a chapter in the *Sushruta-Samhita,* entitled "Instruction in Surgical Operations," which describes the training procedures without which the surgeon's education would be left wanting.

> The preceptor should see that his disciple attends the practice of surgery even if he has already thoroughly mastered the several branches of the science of medicine, or has perused it in its entirety. In all acts connected with surgical operations of incision . . . and injection of oil . . . the pupil should be fully instructed as regards the channels along or into which the operations or applications are to be made. A pupil, otherwise

well read, but uninitiated into the practice of surgery is not competent to take in hand the medical or surgical treatment of a disease. The art of making specific forms of incision should be taught by making cuts in the body of a gourd, watermelon, cucumber. . . . The art of making cuts either in the upward or downward direction should be similarly taught. The art of making incisions should be practically demonstrated by making openings in the body of a full water bag, or in the bladder of a dead animal, or in the side of a leather pouch full of slime or water. The art of scraping should be instructed on a piece of skin on which the hair has been allowed to remain. The art of venesection should be taught on the vein of a dead animal or with the help of a lotus stem. The art of probing and stuffing should be taught on worm-eaten wood, or on the reed of a bamboo, or on the mouth of a dried gourd. The art of extracting should be taught by withdrawing seeds from the kernel of a Jack fruit, as well as by extracting teeth from the jaws of a dead animal. The act of secreting or evacuating should be taught on the surface of a plank covered over with a coat of beeswax, and suturing on pieces of cloth, skin or hide. Similarly, the art of bandaging or ligaturing should be practically learned by tying bandages around the specific limbs and members of a full-sized doll made of stuffed linen. The art of tying up a severed ear lobe should be practically demonstrated on a soft muscle or on flesh, or with the stem of a lotus lilly. The art of cauterizing or applying caustics should be demonstrated on a piece of soft flesh; and, lastly, the art of inserting syringes and injecting enemas into the region of the bladder, or into an ulcerated channel, should be taught by asking the pupil to insert a tube into a lateral fissure of a pitcher, full of water, or into the mouth of a gourd.

An intelligent physician who has tried his prentice hand in surgery, or has learnt the art with the help of things as stated above, or has been instructed in the art of cauterization or blistering by experimenting on things which are most akin, or similar to the parts of members of the human body they are usually applied to, will never lose his presence of mind in his professional practice.

The *Sushruta-Samhita* prescribes, moreover, that after satisfactory initiation of the disciple, he is to be addressed by his preceptor:

Thou shalt renounce lust, anger, greed, ignorance, vanity, egotistic feelings, envy, harshness, parsimony, falsehood, idleness, nay all acts that soil the good name of a man. In proper season thou shalt pare thy nails and clip thy hair and put on the sacred cloth, dyed brownish-yellow, live the life of a truthful self-controlled anchorite, and be obedient and respectful toward thy preceptor. In sleep, in rest, or while moving about—while at meals or in study, and in all acts thou shalt be guided by my directions. . . . Thou shalt help thy professional skill and knowledge, the Brahmanas, thy elders, preceptors and friends, the indigent, the honest, the anchorites, the helpless and those who shall come to thee from a distance, or those who shall live close by, as well as thy relations and kinsmen, to the best of thy knowledge and ability, and thou shalt give them medicine without charging for it any remuneration whatever, and God will bless thee for that. Thou shalt not treat medicinally a professional hunter, a fowler, a habitual sinner, or him who has been degraded in life; and even by so doing thou shalt acquire friends, fame, piety, wealth and all wished-for objects in life, and thy knowledge shall gain publicity.

The training program suggested by Charaka is similar to that of Sushruta. In addition, Charaka urges the young surgeon, "Not for self, not for the fulfillment of any earthly desire or gain, but solely for the good of suffering humanity should you treat your patients, and so excel all."

Another one of Charaka's precepts, "Thou should'st never give out the practices of the patient's house," is evidently an injunction to keep professional secrets.

It is possible that, unlike the Oath of Maimonedes, which is a highly individual statement of creed, the so-called Hippocratic Oath may be more correctly ascribed to have been a pledge taken by members of the School at Cos and the Grecian Temples of Health in the fourth century B.C. It remains one of the most cherished documents in medical heritage. More pertinent from the surgeon's standpoint, however, are the prosaic but exacting passages in the writings of Hippocrates which treat of the requirements of a surgeon. The section "On the Surgery" is illustrative.

It is the business of the physician to know, in the first place, things similar and things dissimilar; those connected with things most important, most easily known, and in anywise known; which are to be seen, touched, and heard; which are to be perceived in the sight, and the touch, and the hearing, and the nose, and the

tongue, and the understanding; which are to be known by all the means we know other things.

The things relating to surgery, are—the patient; the operator; the assistants; the instruments; the light, where and how; how many things, and how; where the body, and the instruments; the time; the manner; the place.

The operator is either sitting or standing, conveniently for himself, for the person operated upon, for the light. There are two kinds of light, the common and the artificial; the common is not at our disposal, the artificial is at our disposal . . . we must turn the part to be operated upon to that which is most brilliant of present and convenient lights . . . thus, the part that is operated upon should be opposite the light, and the operator opposite the part operated upon, except in so far as he does not stand in his own light; for in this case the operator will indeed see, but the thing operated upon will not be seen. With regard to himself: when sitting, his feet should be raised to a direct line with his knees, and nearly in contact with one another; the knees a little higher than the groins, and at some distance from one another, for the elbows to rest upon them. The robe, in a neat and orderly manner, is to be thrown over the elbows and shoulders equally and proportionally. . . . When standing, he must make his inspection, resting firmly and equally on both feet; but he must operate while supporting himself upon either leg, and not the one on the same side with the hand which he makes use of; the knee being raised to the height of the groins as while sitting; and the other measures in like manner. The person operated upon should accommodate the operator with regard to the other parts of his body, either standing, sitting, or lying; so as that he may continue to preserve his figure, avoid sinking down, shrinking from, turning away; and may maintain the figure and position of the part operated upon, during the act of presentation, during the operation, and in the subsequent position.

The nails should be neither longer nor shorter than the points of the fingers; and the surgeon should practice with the extremities of the fingers, the index-finger being usually turned to the thumb; when using the entire hand, it should be prone; when both hands, they should be opposed to one another. It greatly promotes a dextrous use of the fingers when the space between them is large, and when the thumb is opposed to the index. But it is clearly a disease when the thumb is impaired from birth, or when, from a habit contracted during the time of nursing, it is impeded in its motions by the fingers. One should practice all sorts of work with either of them, and with both together (for they are both alike), endeavoring to do them well, elegantly, quickly, without trouble, neatly, and promptly.

The instruments, and when and how they should be prepared, will be treated of afterwards; so that they may not impede the work, and that there may be no difficulty in taking hold of them, with the part of the body which operates. But if another gives them, he must be ready a little beforehand, and do as you direct.

Those about the patient must present the part to be operated upon as may seem proper, and they must hold the rest of body steady, in silence, and listening to the commands of the operator.

One could discuss at great length the many features mentioned in this writing by Hippocrates, and indeed they have been the subject of innumerable commentaries from the time of Galen on. Suffice it to say only that one marvels at how various clauses, from specifications as to the length of the fingernails to posture and decorum while operating, are defined graphically.

Aurelius Cornelius Celsus (25 B.C. to A.D. 50), the Roman physician whose epochal *De Medecina* is one of the most important reference sources of the Greek and Alexandrian Schools, wrote:

Now a surgeon ought to be young, or at all events, not much advanced in years; possessed of a hand that is firm, steady, uniformly devoid of tremor; he should be able to use both hands with equal dexterity; his sight should be penetrating and clear; with a mind undaunted, he should retain so much compassion as may lead him to wish for his patient's recovery, without being so far moved by his shrieks as to induce him to make unnecessary haste, or to cut less than is absolutely expedient; but he ought to complete his operation, in all respects, as though the cries of the sufferer gave rise to no emotion. . . . For my own part, I conceive that the same person may be capable of practicing all the three branches (regimen, drugs, and surgery); but since a division has been effected, I laud that man whose range of information is the most extensive.

Abu Yaqub Ishaq Sulaynam al Israïli, better known as Isaac Judaeus, a surgeon of the tenth century, served under several Egyptian rulers. In his book, *The Guide of Physicians*, many aphorisms are found:

The majority of diseases are cured by nature.

It is in keeping with the character of the physician that he should, in his mode of life, be con-

tent with well prepared food in moderation and be no glutton. Also, it is a shame that he should suffer from a long-drawn-out disease, else the vulgar will say: "If he cannot cure himself, how can he cure others?"

Let not thy mouth condemn, if an accusation be made against a physician, for to every man comes his hour. Let thy deeds be thy praise, rather than find honor in another man's shame.

If the patient does not follow thy directions, or his servants and household do not carry out thy orders with dispatch or treat thee with respect, relinquish the treatment.

Demand thy fee of the patient when his illness is increasing or at its height; when he is healed he forgets what thou hast done for him. The more thou demandest for thy treatment, the more highly thou esteemest thy cure, the higher will thou stand in the eyes of the people. The art will be held of no account only by those whom thou treatest gratuitously.

Visit not the patient too often, nor remain too long with him, unless the treatment demand it, for it is only the fresh encounter which gives pleasure.

Note the recommendation that the physician abstain from derogatory comments against a confrere, an exhortation reiterated frequently in later writings.

Abu'l Qasim Zahrawi, or Albucasis (1013 to 1106), Arabian physician of Cordova in Moorish Spain, authored an encyclopedia on the healing art called *Altasrif,* consisting of some 30 volumes, 3 of which are on surgery. In one of these he remarks:

Surgery is no longer in honor in our country. In its actual decadence, it has disappeared, almost without leaving traces. There remain some vestiges in the writings of the Ancients, but they have corrupted the transcriptions; error and confusion have overrun them, in a manner to render them unintelligible and useless. . . . You know, my children, that surgical operations are divided into two classes: those that benefit the patient, and those that more often kill. . . . It is necessary to be prudent and to abstain from dangerous operations, not to give the ignorant cause for malevolent comment. Conduct yourselves with reserve and caution: have gentleness and perseverance for the patients; follow the good road which leads to favorable and happy outcomes. Abstain from undertaking dangerous and difficult treatments. Avoid that which might injure your honor or your welfare; it is the better part for your reputation and more consistent with your interests in this world and the other.

The archives of the School of Salerno are replete with common-sense advice (such as the *Regimen*), to medical practitioners. A tract of general guidance on manners in Medicine was written around 1100 A.D. by one Archimathaeus, a surgeon about whose life history little is known. A passage from this pamphlet concerns protocol to be observed at the initial visit to a patient:

When you are called to a patient, may the name of God be your help, and may the angel who walked with Tobias be the companion of your mind and body. At your entrance inquire of him who greets you from what disease the sick man suffers and how his illness progresses; this is advisable in order that you come to him not entirely uninformed as to the illness. . . . Again when you reach the house and before you see him, ask if he has seen his confessor, and if he has not done this, arrange for him to do so, or have him promise to do so, for if the sick man hears talk on this subject after he has been examined and the signs of his illness studied, he will begin to despair of it. Entering the sick-room you should have neither proud nor greedy countenance; you should repeat the greeting of those who rise as you enter, and with a gesture seat yourself when they sit down. Next, you may resume the conversation with a few remarks in which you praise the neighborhood, commend the arrangements of the house, if it seems appropriate, or compliment the liberality of the family.

Then turning to the patient you may ask how it goes with him, and have him put out his arm. At first there may be differences, between your own state and that of the patient, either because he is excited at your arrival, or because he is worried about the size of your fee, so that you find the pulse rather confusing; therefore you should consider the pulse only after the patient has become steadier. Take care that he does not lie upon his side nor has his finger over-extended or flexed against his palm. Support his arm with your left hand and observe the pulse for at least 100 beats in order to feel all its variations, and thus you will be able to satisfy the expectant bystanders with words which they are glad to hear.

Next you have the urine brought to you, that the sick man may see you study his illnesses not only from the pulse but from the urine. When examining the urine you should observe its color, substance, quantity, and content; after which you may promise the patient that with the help of God you will cure him. As you go away, however, you should say to his servants that he is in a very bad way, because if he recovers you will receive great credit and praise, and if he dies, they will

remember that you despaired of his health from the beginning. Meanwhile, I urge you not to turn a lingering eye upon his wife, his daughter, or his maid-servant, for this sort of thing blinds the eye of the doctor, averts the favor of God, and makes the doctor abhorrent to the patient and less confident in himself. Be therefore careful in speech, respectable in conduct, attentively seeking Divine aid. If the people of the house invite you to a meal, as often happens, do not seem too much gratified, and do not seek the first place at the table, although it is the custom to give this to the priest or the doctor. Do not criticize the food or drink, and when in the country do not show distaste for country food, for example millet bread, even though you can scarcely control your stomach.

While you eat you may inquire as to the conditions of the patient from anyone who is present, for in this way the sick man will confide in you all the more, since he sees that you do not forget him while seeking your own comfort. When you rise from the table you may mention that you have been well looked after; this too will give pleasure to the patient.

William of Saliceto (1210 to 1277), professor of Surgery at Bologna and later at Verona, wrote similar counsel, with the added admonition, "A wise surgeon will refrain from stealing while he is actually in attendance upon a patient."

Lanfranchi of Milan (1250 to 1315), Saliceto's ablest pupil, was a Surgeon of the Long Robe, and associated with the college of St. Come. Lanfranchi deplored the separation of Medicine from Surgery, a dichotomy which had existed since Avicenna's time.

Good God, why this abandoning of operations by physicians to lay persons, disdaining surgery because they do not know how to operate, an abuse which has reached such a point that the vulgar begin to think the same man cannot know both surgery and medicine? I say, however, that no man can be a good physician who has no knowledge of operative surgery, a knowledge of both branches is essential.

In this stand he was supported by another surgeon, John of Mirfield, who wrote:

Long ago, unless I mistake, physicians used to practice surgery, but nowadays there is a great distinction between surgery and medicine, and this, I fear arises from pride, because physicians disdain to work with their hands, though, indeed, I myself have a suspicion that it is because they do not know how to perform particular operations; and this unfortunate usage has led the public to believe that a man cannot know both subjects, but the well informed are aware that he cannot be a good physician who neglects every part of surgery, and, on the other hand, a surgeon is good for nothing who is without knowledge of medicine.

Lanfranchi's *Cyrurgia Magna* (1296) has the following passage:

It is necessary that a surgeon should have a temperate and moderate disposition, that he should have well-formed fingers, a strong body, not inclined to tremble and with all his members trained to the capable fulfillment of the wishes of his mind. He should be of deep intelligence and of a simple, humble, brave but not audacious disposition. He should be well-grounded in natural science, and should know not only medicine, but every part of philosophy, should know logic well, so as to be able to understand what is written, to talk properly, and to support what he has to say by good reasons.

Henri de Mondeville (1260 to 1320) studied at Montpellier. Graduates from its school of medicine included such celebrities as Arnold of Villanova, John of Arderne, and Guy de Chauliac. De Mondeville achieved eminence in surgery. He was an implacable enemy of charlatanism and empiricism. The following excerpts are from his writings:

A surgeon ought to be fairly bold. He should not quarrel before the laity and although he should operate wisely and prudently he should not undertake any dangerous operation unless he is sure that it is the only way to avoid a greater danger. His limbs, and especially his hands, should be well-shaped with long, delicate and supple fingers which must not be tremulous. He ought to promise a cure to every patient but should tell the parents or friends if there is any danger. He should refuse as far as possible all difficult cases and never interfere with the desperate ones. He may give advice to the poor for the love of God only, but the rich should be made to pay well. He should neither praise himself nor blame others and he should not hate any of his colleagues. He ought to sympathize with his patients in their distress and fall in with their lawful requests so far as they do not interfere with the treatment. Patients, on the other hand, should obey their surgeon implicitly in everything appertaining to their cure. The surgeon's assistants must be loyal to their master and friendly to his patients. They ought not to tell the patient what the surgeon says un-

less the news is pleasant and they should always appear cheerful. They should not be constantly grumbling, because this inspires fear and doubt in the patient.

Many more surgeons know how to cause suppuration than how to heal a wound. Keep your needles sharp and clean or they will infect the wound. Surgery is an integral part of medicine for it is in reality a method of treatment.

Take care to regulate the whole regimen of the patient's life for joy and happiness by promising that he will soon be well, by allowing his relatives and special friends to cheer him and by having someone to tell him jokes, and let him be solaced also by music on the viol or psaltery.

You, then surgeons, if you have operated conscientiously on the rich for a suitable fee, and on the poor for charity, you need not fear fire, rain or wind, you have no need to go into religion, to make pilgrimages, or other acts of the sort, because by your science you have been able to save your souls, live without poverty and die in your homes, live in peace . . . and exult because reward is great in the Heavens. . . .

For good measure, de Mondeville interjected a few items of "horse-sense" reminiscent of the essays of Chalmers Da Costa:

Never dine with a patient who is in your debt, but get your dinner at an inn. Otherwise, he will deduct the cost of his hospitality from your fee.

I have never found anyone so rich, or even so honest . . . who was ready to pay what he had promised unless obligated and convicted.

He also reprimanded surgeons who lacked originality and did not make use of their own initiative and intellect, preferring only to quote their preceptors. He exclaimed contemptuously, "God did not exhaust all His creative powers in making Galen!"

The teachings of Guy de Chauliac (1300 to 1368), Prince of French Surgery during the mediaeval epoch and physician to several Popes, were of greatest authority for a considerable period. His chief work was the *Chirurgia,* written in 1363, in which he enumerates attributes desirable in a surgeon.

The prerequisites of a Surgeon are four in number: first, that he be lettered, second, expert, third, ingenious, fourth, well schooled in Ethics. It is thus required from the start that the Surgeon be lettered, not only in the principles of Surgery, but also of Medicine, both in theory as well as practice. He should be bold in sure things, fearful in hazardous ones, fleeing from bad cures or practices. He should be gracious to patients, benevolent towards his colleagues, sage in his predictions. He should be chaste, sober, compassionate and merciful: neither coveter nor extortionist of money: but receiving moderate stipend, according to his work, the ability of the patient, the quality of the issue or event, and his dignity.

The most prominent British surgeon in Chaucer's time was John of Arderne, or Arden (1307 to 1380), who referred to himself as "chirurgicus inter medicos," a surgeon among physicians. He was the first to revive the healing art of Surgery in England. One of his most famous articles, entitled *Of ye manere of ye leche,* expounds on the methods whereby a surgical practice may be conducted properly. Its influence was far-reaching in that critical period of surgical history. The principles laid down by John of Arderne for the guidance of the leech (physician) in regard to his patients as well as in his dealings with his colleagues cannot be held in too high esteem. It would surely be well if we could at all times act in the same gentle manner towards our brethren in the profession, and answer courteously when asked about them, "I learned nought nor have I heard of him but good and honest."

First, it behooves him that will profit in his craft, that he set God afore evermore in all his works, and evermore call meekly with heart and mouth His help. He should sometime visit of his own willingness poor men in his midst, that they by their prayers may get him grace of the Holy Ghost. He should not be found rash or boastful in his speech or his deeds. He should abstain from much speech, especially among great men. He should answer warily to things asked, that he be not mistaken in his words. For, if his works be oft time known, if he discord from his words and his promises, he shall be unworthy and blemish his own good fame: whereupon says a verse, "Work overcome thy word, for boasting lessens good report." A leech should not laugh or play too much. And also, as much as he may without harm, he should flee the fellowship of knaves and of disreputable persons. He should evermore be occupied in things that pertain to his craft. He should either read, or study, or write, or pray, for a leech worships the exercise of books; for which he shall both be esteemed and be more wise. Above all this, it will profit him to be found evermore sober, for drunkenness destroys all virtue and brings it to nought; as says a wise man,

"Drunkenness breaks what wisdom touches." Be he content in strange places of meats and drinks that he finds, using measure in all things; for the wise man says, "As it profits to put measure in all things that are, so without measure perish all things that are." Scorn he no man, for of that it is said, "He that scorns other men shall not go away unscorned." If there be made speech to him of any leech, neither set he at him, nor praise him too much or commend him, but thus may he courteously answer, "I have not any knowledge of him; but I learned nought nor have I heard of him but good and honest;" and of this shall honor and thankings of each party increase and multiply to him; after this, honor is in the honorant and not in the honored. Consider he not overopenly the lady or the daughters or other fair women in great men's houses, nor proffer to kiss, or touch, neither privately nor openly, their breasts or their hands or their hair, that he run not into the indignation of the lord nor of none of his household. Inasmuch as he may, grieve he no servants, but get he their love and their good will. He should abstain from harlotry in words as well as in deeds in every place, for if he becomes used to harlotry in private places, sometime in open place, there may fall to him habit of evil usage.

When sick men, or any of their relatives, come to the leech to ask help or counsel of him, he should not be overfriendly or overfamiliar, but act in bearing according to the requirements of the persons, to some reverently, to some commonly, for according to wise men," over-familiarity breeds despising." Also, it is of advantage that he have proper excuses, that he may not incline to their asking, without slighting or causing indignation of some great man or friend. Feign he hurt or illness, or some other convenient cause by which he may likely be excused. Therefore if he will favor to any man's asking, make he covenant for his travail and take it before hand. But the leech should take care that he give no certain answer in any case before seeing first the sickness and its nature; and when he has seen and assayed it, although it may seem to him that the sick person may be healed, nevertheless he shall make prognostication to the patient the perils to come if the cure be deferred. . . .

And if the patients or their friends or servants ask by how much time he hopes to heal it, always let the leech name the double of what he estimates. That is, if the leech hopes to heal the patient by twenty weeks, which is the common course of curing, add he so many more; for it is better that the term be lengthened than the cure; for prolongation of the cure gives cause of despairing to the patients, when trust in the leech is most hope of health. And if the patient consider or wonder or ask, why that he put him so long a time of curing, since he healed him by half? Answer he, it was because the patient was strong-hearted and suffered well sharp things, and that he was of good complexion, and had able flesh to heal, and feign he other causes pleasable to the patient, for patients of such words are proud and delighted.

Also, it disposes a leech that in clothes and other apparel he be honest, not likening himself in apparel or bearing to minstrels, but in clothing and bearing follow the manner of clerks; for it seems any discreet man clad with clerks' clothing is worthy to occupy gentlemen's boards. The leech should also have clean hands, and well-shaped nails cleansed from all blackness and filth. He should be courteous at lord's boards, and not displease in words or deeds the guests sitting by. He should hear many things but speak little, for as a wise man said, "It benefits more to use the ears than the tongue." And in another place, "If thou had been still, thou would have been thought a philosopher." And when he shall speak, be the words short, and as much as he may, fair and reasonable and without swearing. Beware that there never be found double words in his mouth; for if he be found true in his words, few or none shall doubt in his deeds.

The book of Jerome of Brunswick (1450 to 1533) has the distinction of being the first illustrated treatise on surgery of its kind printed in the English language. Jerome was an unrelenting foe of the barber-surgeons. In the prologue, Jerome's summing up of the value of the consultation bears repeating:

First, you learn by chance things that you seldom or never have seen before. Secondarily, if ought in your hands happen to misfortune, that you may quickly amend it. Thirdly, that the wounded person have less grudge or mistrust in you. Fourthly, when the cure has good speed, then you be partaker of all the honour thereof; and if misfortune fall between your hands, then every man is bound to bear the charge of your hinder and losses which would be too much for you alone. Fifthly, for this wise deed you be praised of all them that be discrete or learned men, who will speak of you saying you desire to learn, and will not that any man should be by you negligently spilt or perished. And thus may you come to your purpose with honesty and pleasure, which else might turn to your great shame and displeasure.

Heinrich von Pfolspeundt was a notable Bavarian army surgeon of the mid-fifteenth century. His *Buch der Bundth-Ertznei* is the

oldest surgical book in the German language. Pfolspeundt must have had a flair for the sacerdotal in surgery:

> Firstly, I advise anyone who wishes to work in this art and to heal, that he should not go to a wounded or sick person in the early morning or treat him before he has heard Mass, so far as is possible, unless there is great need, but he shall pray to the Good Lord to bless the wounds, to say a Pater Noster and an Ave Maria and confess his faith, so that strength and wisdome be given him to heal the people. . . .
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> And he should guard himself against drunkenness when he is to treat patients, for because of it they may easily be neglected, and the doctor would be guilty of that and be punished by God. And especially, he should guard himself, if he has eaten onions or beans, or slept the previous night with an unclean woman . . . against breathing into anyone's wound. Also, he should bind with clean white cloths, for if they are not clean, harm results. He should also wash his hands before he treats anyone. Also he should love healing for the sake of God, if he is able; also if the doctor knows himself to be unclean, he should not look actively into the wounds . . . else mischief and harm arises. . . . And keep people protected, or you will have to do penance before God, if you are to blame."

Felix Wirtz (1510? to 1580), an itinerant Swiss surgeon, was an admirer of Paracelsus and, like him, was an "angry young man" of Surgery. Although he was not exactly a burner of books, as Paracelsus, he had the courage to explode publicly to students, "What do you suppose I care whether Galen's or Avicenna's or Guy de Chauliac's opinion does or does not agree with mine?"

Moreover, unlike Paracelsus, whose writings were imbued with necromancy and metaphysics, Wirtz was almost brutally practical. He was scornful on matters of surgical theory, remarking tartly, "Surgery depends more on dexterity than on twaddle."

Ambroise Paré (1510 to 1590), paragon of surgeons in the Renaissance, is probably second only to John Hunter for his role in raising surgery to loftier terrain than it had been previously. He carved for himself a niche in immortality with the modest words, "Je l'ay pansé, Dieu le guarit." The introduction of his tome, *A la Chirurgie,* contains various topics defining the integral role of surgery in medicine. He also stated: "As for me, I am of the same opinion as Celsus, who urges the Surgeon to be assured of his tasks, and not be timid and afraid; so that when he operates with his hands, he should heed neither the clamor of the patient nor the assistants, slowed down no more than avoidable, and not hastening unnecessarily, but accomplishing his purpose without regard for those who in their ignorance despise the Surgeon. . . ."

Juan Rodrigo de Castel-Branco, or Amatus Lusitanus (1536 to 1614), was a Portuguese Jewish surgeon who fled the Inquisition from his native country, only to be summoned as consultant during the illness of Pope Julius III. The Oath of Amatus, published in his *Centuriae,* is similar to the Maimonedic Oath in its personal theme. It is one of the noblest compositions in the annals of surgical literature, and should be in print more frequently than it has been.

> I swear by the Eternal God and by His ten most holy commandments, which were given on Mount Sinai through Moses as lawgiver after the people had been freed from their bondage in Egypt, that I have never, at any time, done anything in these my treatments save what inviolate faith handed down to posterity; that I have never feigned anything, added anything or changed anything for the sake of gain; that I have always striven after this one thing, namely, that benefit might spread forth to mankind; that I have praised no one, and censured no one merely to indulge in private passions, unless zeal for truth demanded this. If I lie, may I incur the eternal wrath of God and his angel Raphael, and may I not succeed according to my intent in any of my medical work.
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> Concerning the remuneration, furthermore, which is commonly given to physicians, I have not been anxious for this, but I have treated many, not only zealously, but even without pay; and have unselfishly and unswervingly refused several rewards offered by many people; and have rather sought that the sick might, by my care and diligence, recover their lost health than that I might become richer by their liberality. All men have been considered equal by me of whatever religion they were, whether Hebrews, Christians, or the followers of the Moslem faith.
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> As concerns loftiness of station, that has never been a matter of concern to me, and I have accorded the same care to the poor as to those

born in exalted rank. I have never brought about sickness; in diagnosis I have always said what I thought to be true. I have unduly favored no vendors of drugs, except perhaps those whom I knew to surpass the others by reason of their skill in their art or because of their natural qualities of mind. In prescribing drugs I have exercised moderation in proportion as the powers of the sick man allowed. I have revealed to no one a secret entrusted to me; I have given no one a fatal draught. No woman has ever brought about an abortion by my aid; nothing base has been committed by me in my house where I was practicing; in short, nothing has been done by me which might be considered unbecoming an excellent and famous physician.

I have always held up to myself Hippocrates and Galen, the fathers of the medical art, as examples worthy of being followed by me, and the records of many other excellent men in the medical art have not been scorned by me. In my method of studying, I have been so eager that no task, however difficult, could lead me away from the reading of good authors, neither the loss of private fortune, nor frequent journeys, nor yet exile, which, as befits a philosopher, I have thus far borne with calm and invincible courage. And the many students which I have thus far had I have always considered my sons, have taught them very frankly, and have urged them to strive to conduct themselves like good men.

I have published my books on medical matters with no desire for profit, but I have had regard for this one thing, namely, that I might, in some measure, provide for the health of mankind. Whether I have succeeded in this, I leave to the judgment of others, At all events, I have held this always before me, and have given it chief place in my prayers.

William Bulleine, educated at Cambridge, was a London surgeon during the reign of King Henry VIII. He died in 1576, 14 years after publishing his interesting monograph, *A little dialogue between two men, the one called Sorenes and the other Chirurgi: concernyng Apostumacions and Woundes their causes and also their cures.* His notion of a worthy surgeon was expressed as follows:

> Eight things or properties of a good Chirurgeon. He must begin first in youth with good learning, and exercise in this noble art; he must also be cleanly, nimble-handed, sharp-sighted, pregnant-witted, bold-spirted, cleanly-appareled, pitiful-hearted, but not womanly-affectionated to weep or tremble when he sees broken bones or bloody wounds, neither must he give place to cry of his sore Patient, for soft Chirurgeons make foul sores. On the other hand, he may not play the part of a Butcher to cut, rend, or tear the body of mankind. For although it be frail, sore, and weak, yet it is the pleasure of God to call it his Temple, his Instrument, and dwelling-place, and the Philosopher does call it Orbiculus, that is, a little world. That is, Nature is the worker, the Physician is but his minister. Therefore the Chirurgical Physician is Nature's Servant.

Thomas Gale (1507 to 1587), was a contemporary of William Bulleine and Ambroise Paré. He saw much service as a military surgeon, greatly lamented the state of the profession in his day, and was a prime moving spirit in demanding legislation to curb effectively the practicing of surgery by unitiated and unschooled individuals. In 1563 he published the treatise, *An institution of a Chirurgian conteyning the sure Groundes and Principles of Chirurgiry moste necessary and mete for all those that will attayne the arte perfectly.* This was a well-digested work intended to ground the young student in ethics, and to expose that empirical kind of practice which busied itself with the mere collection of forms of therapy, without adequate knowledge of their proper application. The situation prevailing in this period of the reign of the Tudors is deplored by Gale:

> The greater number of Chirurgeons (I mean those that are there unto lawfully called), are so rude and unskilful in their art because they have no method, no exact way, or yet order in learning the grounds and principles of Chirurgery. . . . So that they are confused in their studies and make rather a rude chaos than a perfect art of Chirurgery. For now it is come to this point, that if they can get this receipt (prescription) and that receipt, as they term it, they think they need no further study. So that the more receipts he has, the greater a Chirurgeon he thinks himself to be; such ignorance now reigns that receipts bear the bell; theory of Chirurgery is quite forsaken or not regarded. . . .

Gale also gives an account of the qualifications and tenets which should be inherent in the model surgeon. The Guido he alludes to was Guido Guidi, or Vidius, a coeval educator who was Italy's leading surgeon, and after whom the Vidian canal and nerve are named.

Guido requires four things in him that is or would be a Chirurgeon. First, that he should be lettered, secondly, that he should be expert, thirdly, that he be ingenious, and last, that he be virtuous and well-mannered. . . . And touching these four points, note first when Guido says he must be lettered, he does mean that he should be learned, and that chiefly in such doctrine as is in his art requisite. That is at the least, that he can write, read, and understand the mind of Latin authours. If he had knowledge in geometry for making his incision, for curing fractures and luxations, and also in curing malignant ulcers; knowing what figure would most speedily unite, and join the lips of the ulcer; it would be very commendable. Natural Philosophy is a goodly adornment to the Chirurgeon, for it shows him what results when diverse and sundry simples are mixed together. But I will go to the second point, he must be expert, that is he must be garnished with much and long experience, which is excogitated by firm and certain reasons and by them also confirmed; otherwise he is to be accompted rude, and an empiric, if he has no reason annexed and joined to his experience.

Thirdly, says Guido, he must be ingenious, unto which there are five things principally required. First, is the ready and good conceiving; then, a firm and sure memory; next, a sound and right judgement; after, an easy calling things to mind which we have heard or seen; and last, a lively and sharp readiness in finding and inventing remedies.

The manners which Guido would have in a Chirurgeon are reckoned of Hippocrates and Celsus, which briefly I will number; he must be bold and without fear in such cures as are without peril, and which necessity requires. Also in cures that be doubtful, not too risky and hasty, to be gentle and courteous toward the sick patient, to be friendly and loving toward those of his profession. Also wise and circumspect in prognostications. Last of all, he must be chaste and temperate of body, merciful toward the poor, and not too greedy of money. And this is sufficient touching the description of he that must be admitted in Chirurgery.

In relation to the patient, Gale observes:

The Chirurgeon must also in these his operations observe six things principally. First, that he does it safely, and without hurt and damage to the patient. Secondly, that he does not detract time or let sleep good occasions offered in working, but with such speed as art shall suffer, let him finish his cure. Thirdly, that he would gently, courteously, and with as little pain to the patient as conveniently he may, and not roughly, butcherly, rudely. . . . Fourthly, that he be as free from craftiness and deceit in all his workings as the East is from the West. Fifthly, that he take no cure in hand for lucre or gains-sake only, but rather for an honest and competent reward with a godly affection to do his diligence. Last of all, that he make no warranty of such sicknesses as are incurable, as to cure a cancer not ulcerated, or elephantiasis confirmed; but circumspectly to consider what the effect is, and promise no more than art can perform. . . .

This compilation, then, presents exemplary ideas of great men during the infancy of surgery. They constitute part of our legacy and are worthy of recapitulation. Many of the tenets and wisdom expressed therein are as relevant in our day as when they were penned; for, in the words of a Chinese proverb, "The ancients saw not the modern moon, but the modern moon shone on the ancients."

ERRATUM

In the paper "Duplication of the Stomach," by George Abrami, M.B., Ch.B., and Wallace M. Dennison, M.D., in the June, 1961, issue of SURGERY, Figs. 5 and 6 were reversed. The legend appearing under Fig. 5 should be with Fig. 6 and vice versa.